DEVELOPMENT OF BUCCAL ADHESIVE TABLETS OF OLMESARTAN MEDOXOMIL

Dissertation submitted to

THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSITY,

CHENNAI-32

In partial fulfillment of the requirement

for the award of degree of

MASTER OF PHARMACY IN PHARMACEUTICS

Submitted By

(Reg. No: 261211306)

DEPARTMENT OF PHARMACEUTICS

COLLEGE OF PHARMACY

MADURAI MEDICAL COLLEGE

MADURAI – 625020

APRIL -2014

CERTIFICATE

بسم الله الرحمن الرحيم
In the Name of Allāh, the Most Gracious, the Most Merciful

Prof. Dr. A. ABDUL HASAN SATHALI, M.Pharm., Ph.D,
Principal (I/C),
College of Pharmacy,
Madurai Medical College,
Madurai -625 020, (TN), India.
Email: drabdulhasan@rediffmail.com
Mob: 09443475400

Res: 19, Nallamani Nagar,
Lordu Nagar 12th Street,
K-Pudur,
Madurai – 625007. (TN), India.

CERTIFICATE

This is to certify that the Dissertation entitled **"Development of Buccal Adhesive Tablets of Olmesartan Medoxomil"** submitted by **Mr.J.Rajeshkumar (M.Pharm II Year)** in partial fulfillment of the requirement for the degree of **Master of Pharmacy** in **Pharmaceutics** is a bonafide work carried out by him, under my guidance and supervision during the academic year 2013 – 2014 in the Department of Pharmaceutics, College of Pharmacy, Madurai Medical College, Madurai-20.

This dissertation is forwarded to the Controller of Examinations, The Tamilnadu Dr. M.G.R. Medical University,Chennai-32.

Place: Madurai

Date: **(Prof. Dr.A. Abdul Hasan Sathali, M.Pharm., Ph.D.,)**

ACKNOWLEDGEMENT

ACKNOWLEDGEMENT

It is my pleasure to express my respectful regards and thanks to ***Dr. B. Santhakumar. M. Sc (F. Sc), MD (F.M), PGDMLE, Dip. N.B (F.M).,*** *Dean, Madurai Medical College, Madurai for providing all kinds of supportive facilities required to carry out my project work.*

It is my immense pleasure and honour to express my deep sense of gratitude and heartfelt thanks to ***Prof.Dr. A. Abdul Hasan Sathali, M.Pharm., Ph.D.,*** *Principal (I/C), College of Pharmacy, Madurai Medical College, Madurai, for his excellence in guidance, contribution and encouragement which helped me in the successful completion of each and every stage of my project work.*

I express my heartiest thanks to ***Medoform (P) Ltd, Chennai,*** *for providing the drug Olmesartan Medoxomil as gift sample,* ***SD Fine Chemicals ,Mumbai,*** *(Carbopol 934P) and* ***Steril-gene Life Sciences (P) Ltd, Pondicherry,*** *(HPMC K15M, Xanthan gum, CMC Sodium, Lactose and Mannitol) for providing chemicals to carry out my project work.*

With immense pleasure I record here my indebtedness and hearty thanks to ***teaching and non teaching staff of*** *Department of pharmaceutics for their support and valuable suggestions throughout my project work.*

I also extend my thanks to ***JSS College of pharmacy, Ooty and, PSG College of Pharmacy, Coimbatore*** *for permitting me to carry out DSC and IR studies connected to my dissertation work.*

I would like to give my sincere thanks to my classmates ***Mr. P. Arjunkumar., Mr. P. Kanniyappan., Mr. A. Manikkavasagan., Mrs. S. Ponnammal Asmi., Mr. C. Pravinkumar., Mr. M. Ramanathan., Mr. Sankar Ganesh., and Mr. S. Sudhakar.,*** *for their timely help and co-operation.*

I would like to thank my seniors and juniors (PG) for their moral support to carry out my project work.

I also extend my thanks to all the staff members and P.G. Students of Department of Pharmaceutical Chemistry and Pharmacognosy for their Co-operation.

I would like to express my gratitudes to ***my parents, brothers and friends*** *for their moral support to successfully carryout my project work.*

I am extremely thankful to the staffs of ***Laser Point*** *for their kind co-operation regarding printing and binding of this project work.*

Place: Madurai

Date: **(J.RAJESHKUMAR)**

CONTENTS

CONTENTS

CHAPTER NO.	TITLE	PAGE NO.
I	INTRODUCTION	1
II	BUCCAL MUCOADHESIVE DRUG DELIVERY- A REVIEW	6
III	LITERATURE REVIEW	17
IV	AIM OF THE WORK	37
V	PLAN OF WORK	39
VI	MATERIALS AND EQUIPMENTS	41
VII	DRUG PROFILE	43
VIII	EXCIPIENTS PROFILE	50
IX	EXPERIMENTAL PROTOCOL	67
X	RESULTS AND DISCUSSION TABLES & FIGURES	78
XI	SUMMARY AND CONCLUSION	92
	REFERENCES	

CHAPTER I

INTRODUCTION

CHAPTER I

INTRODUCTION

ORAL CONTROLLED DRUG DELIVERY SYSTEMS

Oral drug delivery systems

The most preferred route of drug administration for systemic delivery of drugs is oral route. More than 50% of drug delivery systems available in the market are oral drug delivery systems. These systems have the obvious advantages of case of administration and patient acceptance. One would always like to have ideal drug delivery systems that will possess two main properties,

1. It will be a single dose for the whole duration of treatment,
2. It will deliver the active drug directly at the site of action.

It offers advantages like,

- Ease of administration
- Patient compliance
- Flexibility in formulation("Novel drug delivery systems" by Chein Y.W, 1982, 2nd edition)

The controlled drug release

- Controlled drug delivery is one which delivers the drug at a predetermined rate, for locally or systemically, for a specified period of time.
- Continuous oral delivery of drugs at predictable & reproducible kinetics for predetermined period throughout the course of GIT.

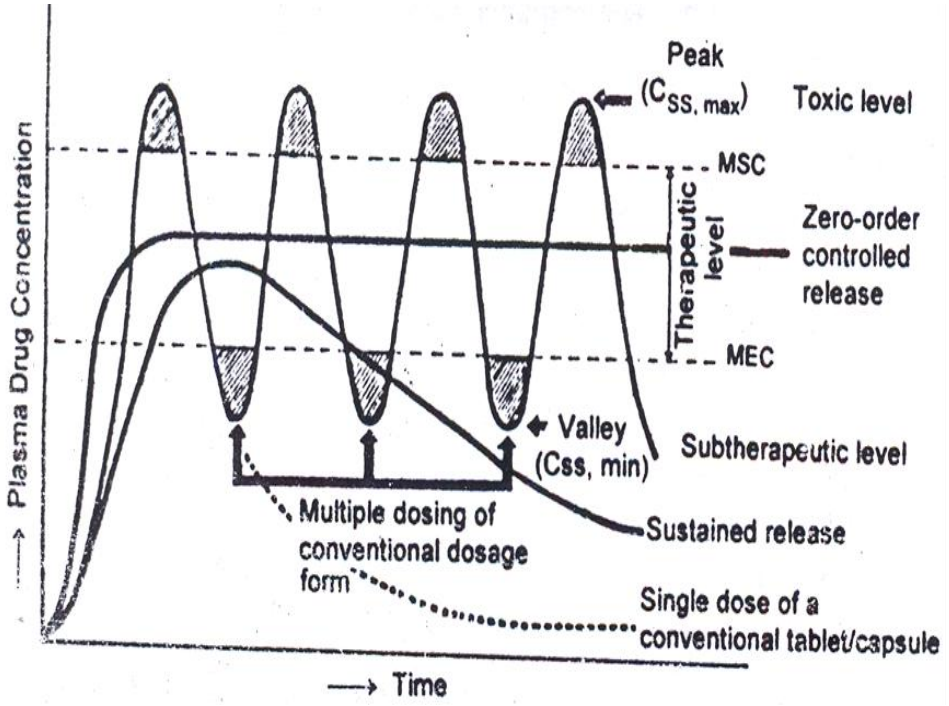


FIGURE 1

Oral Controlled Release Formulation

Oral route has been the commonly selected and most convenient for the drug delivery.

Most of the oral controlled drug delivery systems rely on diffusion, dissolution or combination of both mechanisms, to release the drug in a controlled manner to the Gastrointestinal Tract (GIT).

Targeting systems are either releasing drug in controlled manner or in one burst at the specific area.("Targeted and controlled drug delivery" by Vyas S.P., Khar R K) The goal of a targeted oral drug delivery system (TODDS) is to achieve better therapeutics success compared to conventional dosage form. This can be achieved by improving the pharmacokinetic profile, patient convenience and compliance in therapy, some of the advantages of TODDS are:

- Reduced dosing frequency

- Better patient convenience and compliance
- Reduced GI side effects and other toxic effects.
- Less fluctuating plasma drug level
- More uniform drug effect
- Less total dose
- Better stability of the drug.

On the other hand TODDS suffer from a number of potential disadvantages:

- ❖ Higher cost
- ❖ Relatively poor in vitro-in vivo correlation
- ❖ Possible dose dumping
- ❖ Reduced potential for dose change or withdrawal in the event of toxicity

Targeting of drugs through oral route involves control of time of release or location of release. On the basis of environmental, anatomical and physiological factors these drug delivery system can be classified with respect to target site as follows:

- ➢ Systems targeted to stomach/duodenum
- ➢ Systems targeted to small intestine
- ➢ Systems targeted to large intestine/colon
- ➢ Systems targeted to lymphatic.

Factors influencing the design and performance of controlled drug deliverysystem

Biopharmaceutics characteristics of drug

- Molecular weight of the drug
- Aqueous solubility of the drug
- Apparent partition coefficient

- Drug pKa and ionization physiological pH
- Drug stability
- Mechanism and site of absorption
- Route of administration.

Pharmacokinetic characteristic of the drug

- ✓ Absorption rate
- ✓ Elimination half life
- ✓ Rate of metabolism
- ✓ Dosage form index

Pharmacodynamic characteristic of the drug

- ➢ Therapeutic range
- ➢ therapeutic index
- ➢ Plasma–concentration–response relationship.

Advantages of controlled drug delivery systems

- ▪ Improved patient convenience and compliance
- ▪ Reduction in fluctuation in steady state levels.
- ▪ Increased safety margin of high potency drugs.
- ▪ Reduction in dose.
- ▪ Reduction in health care cost.
- ▪ Total dose is low.
- ▪ Reduced GI side effects.
- ▪ Better patient acceptance and compliance.
- ▪ Less fluctuation at plasma drug levels.
- ▪ More uniform drug effect
- ▪ Improved efficacy/safety ratio.

- Dose dumping.
- Reduced potential for accurate dose adjustment.
- Need of additional patient education.
- Reduced dosing frequency.

Disadvantages of controlled drug delivery systems

- Decreased systemic availability.
- Poor *invitro-invivo* correlations.
- Chances of dose dumping.
- Dose withdrawal is not possible.
- Higher cost of formulation.

CHAPTER II

BUCCAL MUCOADHESIVE DRUG DELIVERY-A REVIEW

CHAPTER II

BUCCAL DRUG DELIVERY SYSTEM - A REVIEW

Buccal route of drug delivery is a good alternative, amongst the various routes of drug delivery. Oral route is perhaps the most preferred for the patients. Within the oral mucosal cavity, the buccal region offers an attractive route of administration for systemic drug delivery. However, oral administration of drugs has disadvantages such as hepatic first pass metabolism and enzymatic degradation within the GI tract, that prohibit oral administration of certain classes of drugs especially peptides and proteins.

Buccal drug delivery offer distinct advantages over oral administration for systemic drug delivery. These advantages include possible bypass of first pass effect, avoidance of pre-systemic elimination within the GI tract, these factors make the oral mucosal cavity a very attractive and feasible site for systemic drug delivery. Considering the low patient compliance of rectal, vaginal, sublingual and nasal drug delivery for controlled release, the buccal mucosa has rich blood supply and it is relatively permeable.

The buccal mucosa lines the inner cheek and buccal formulations are placed in the mouth between the upper gingival (gums) and cheek to treat local and systemic conditions. (Pankil A. Gandhi et al., 2011)

ADVANTAGES OF BUCCAL DRUG DELIVERY

- Bypass the gastrointestinal tract and hepatic portal system, increasing the bioavailability of orally administered drugs that otherwise undergo hepatic first-pass metabolism.
- Improved patient compliance due to the elimination of associated pain with injections.

- Sustained drug delivery.
- A relatively rapid onset of action can be achieved relative to the oral route and the formulation can be removed if therapy is required to be discontinued.
- Increased ease of drug administration
- The large contact surface of the oral cavity contributes to rapid and extensive drug absorption
- Extent of perfusion is more therefore quick and effective absorption.
- Nausea and vomiting are greatly avoided.
- Used in case of unconscious and less cooperative patients.
- Drugs, which show poor bioavailability via the oral route, can be administered conveniently.

Eg: Drugs, which are unstable in the acidic environment of the stomach or are destroyed by the enzymatic or alkaline environment of the intestine.

LIMITATIONS OF BUCCAL DRUG DELIVERY:

- Drugs which irritate oral mucosa or have bitter taste, or cause allergic reactions, discoloration of teeth cannot be formulated.
- If formulation contains antimicrobial agents, affects the natural microbes in the buccal cavity.
- The patient cannot eat/drink/speak.
- Only those drugs which are absorbed by passive diffusion can be administered by this route.
- Drugs which are unstable at buccal pH cannot be administered by this route.
- Swallowing of saliva can also potentially lead to the loss of dissolved or suspended drug

- Low permeability of the buccal membrane, specifically when compared to the sublingual membrane. (Pankil A. Gandhi et al., 2011)

OVERVIEW OF BUCCAL MUCOSA

A. Structure

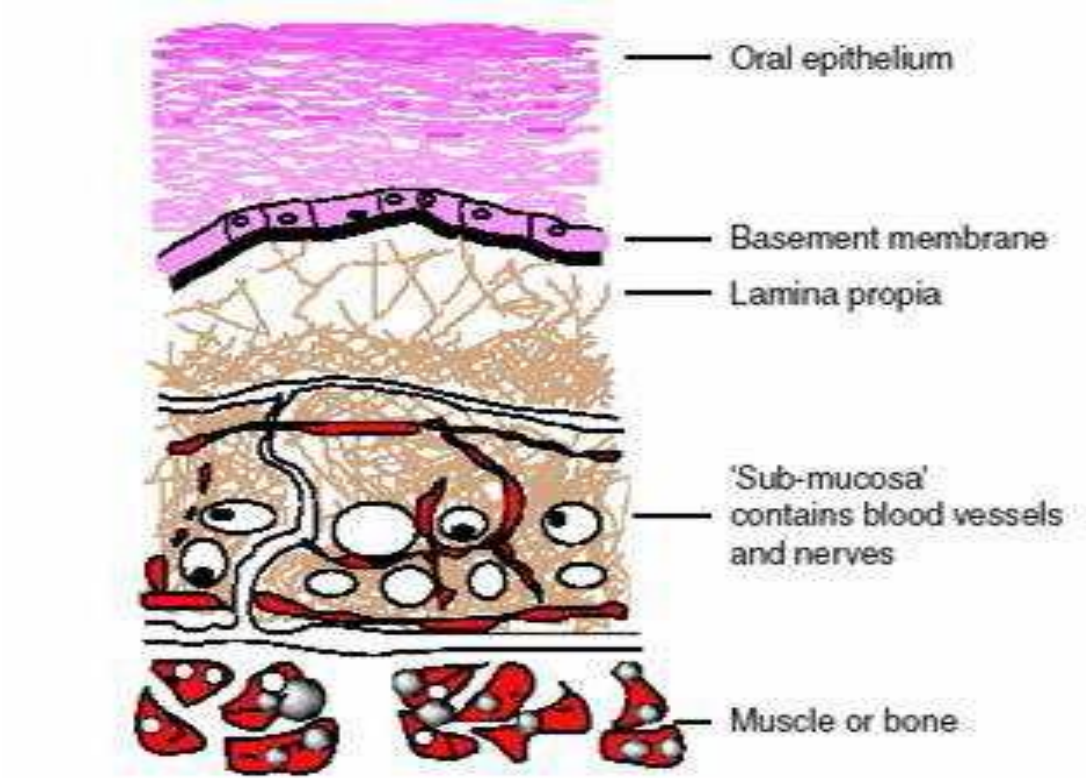


FIGURE 2: CROSS SECTION OF ORAL MUCOSA

The oral mucosa is anatomically divided into

1) Epithelium

2) Basement membrane and Connective tissues

1) Epithelium:

The epithelium consists of approximately 40–50 layers of stratified squamous epithelial cells having thickness 500-800µm. The epithelium of the oral mucosa serves as a protective covering for the tissues and a barrier to the entry of foreign materials. These functions are reflected in the organization of the epithelium in which individual epithelial cells are closely opposed and stratified so there are a

number of layers that show a sequence of differentiation. The uppermost layers form a surface that is resistant to physical insult and to penetration by foreign substances. Membrane Coating Granules (MCG) are spherical or oval organelles (100–300 nm in diameter). (Pankil A. Gandhi et al., 2011)

2) Basement Membrane and Connective Tissue

The basement membrane (BM) is a continuous layer of extracellular materials and forms a boundary between the basal layer of epithelium and the connective tissues. This basal complex anchors the epithelium to the connective tissue and supplements the barrier function of the superficial layers of the epithelium to prevent some large molecules from passing the oral mucosa. The bulk of connective tissue consists of a collagen fiber network, the organization of which determines mechanical stability, resistance to deformation, and extendibility of the tissue. (Pankil A. Gandhi et al., 2011)

Permeability:-

It is estimated that the permeability of the buccal mucosa is 4-4000 times greater than the skin. There are considerable differences in permeability between different region of the oral cavity because of diverse structures and functions of the different oral mucosa. In general, the permeability of the oral mucosa decreases in the order of sublingual greater than buccal, and buccal greater than palatal**.** This rank order is based on the relative thickness and degree of keratinization of these tissues, with the sublingual mucosa being relatively thin and non-keratinized, the buccal thicker and non-keratinized, and the palatal intermediate in thickness but keratinized. In buccal mucosa two routes of passive transport are found one involves the transport of compounds through the intercellular space between the cells (paracellular) and other involves passage into and across the cells (transcellular).

B. Environment

The oral cavity is marked by the presence of saliva produced by the salivary glands and mucus which is secreted by the major and minor salivary glands as part of saliva. (Santanu Roychowdhury et al., 2011)

The mucus layer

Mucus is a translucent and viscid secretion which forms a thin, continuous gel blanket adherent to the mucosal epithelial surface. The mean thickness of this layer varies from about 50 to 450 m in humans. It is secreted by the goblet cells lining the epithelia or by special exocrine glands with mucus cells.

Functions of mucus layer

The Primary functions of the mucus layer are:

i. **Protective:** Resulting particularly from its hydrophobicity and protecting the mucosa from the diffusion of hydrochloric acid from the lumen to the epithelial surface.

ii. **Barrier:** The role of the mucus layer as a barrier in tissue absorption of drugs and other substrates is well known as it influences the bioavailability of drug.

iii. **Adhesion:** Mucus has strong cohesional properties and firmly binds to the epithelial cell surface as a continuous gel layer.

iv. **Lubrication**: An important role of the mucus layer is to keep the mucosal membrane moist.

PHYSIOLOGICAL FACTORS AFFECTING BUCCAL BIOAVAILABILITY

1. Inherent permeability of the epithelium Thickness of epithelium
2. Blood supply
3. Metabolic activity

4. Saliva and mucus
5. Ability to retain delivery system
6. Species differences
7. Transport routes and mechanisms (Gupta S.K et al., 2011)

BUCCAL ROUTES OF DRUG ABSORPTION

There are two permeation pathways for passive drug transport across the oral mucosa:

- Paracellular routes
- Transcellular routes.

Permeants can use these two routes simultaneously, but one route is usually preferred over the other depending on the physicochemical properties of the diffusant. Since the intercellular spaces and cytoplasm are hydrophilic in character, lipophilic compounds would have low solubilities in this environment. The cell membrane, however, is rather lipophilic in nature and hydrophilic solutes will have difficulty permeating through the cell membrane due to a squat partition coefficient. Therefore, the intercellular spaces pose as the main barrier to permeation of lipophilic compounds and the cell membrane acts as the major transport barrier for hydrophilic compounds.

THEORIES OF MUCOADHESION:

Several theories have been put forward to explain the mechanism of polymer–mucus interactions that lead to mucoadhesion. To start with, the sequential events that occur during bioadhesion include an intimate contact between the bioadhesive polymer and the biological tissue due to proper wetting of the bioadhesive surface and swelling of the bioadhesive.

1.Electronic Theory:

The adhesive polymer and mucus typically have different electronic characteristics. When these two surfaces come in contact, a double layer of electrical charge forms at the interface, and then adhesion develops due to the attractive force from electron transfer across the electrical double layer.

2. Adsorption Theory:

The adsorption theory of bioadhesion proposes that adhesion of a polymer to a biological tissue results from:

(i) primary chemical bonds that are somewhat permanent and therefore undesirable in bioadhesion

(ii) van der Waals, hydrogen, hydrophobic and electrostatic forces, which form secondary chemical bonds.

3. Wetting Theory:

Primary application to liquid bioadhesive system, the wetting theory emphasizes the intimate contact between the adhesive and mucus. Thus, a wetting surface is controlled by structural similarity, degree of cross linking of the adhesive polymer, or use of a surfactant.

The work of adhesion [expressed in terms of surface and interfacial tension (Y) being defined as energy per cm2 released when an interface is formed.]

According to Dupres equation work of adhesion is given by

$$Wa = YA + YB – YAB$$

Where,

A & B refer to the biological membranes and the bioadhesive formulation respectively.

The work of cohesion is given by:

$$Wc = 2YA \text{ or } YB$$

For a bioadhesive material B spreading on a biological substrate, the spreading coefficient is given by:

$$SB/A = YA – (YB+YAB)$$

SB/A should be positive for a bioadhesive material to adhere to a biological membrane.

4. Diffusion Theory:

The essence of this theory is that chains of the adhesive and the substrate interpenetrate one another to a sufficient depth to create a semi permanent adhesive bond. The penetration rate depends on the diffusion coefficient of both interacting polymers, and the diffusion co-efficient is known to depend on molecular weight and cross-linking density. In addition, segment mobility, flexibility of the bioadhesive polymer, mucus glycoprotein, and the expanded nature of both network are important parameters that need to be considered.

5.Fracture:

Fracture theory of adhesion is related to separation of two surfaces after adhesion. The fracture strength is equivalent to adhesive strength as given by

$$G = (E\varepsilon. /L)\ ½$$

Where,

E- Young’s modules of elasticity

ε- Fracture energy

L- Critical crack length when two surfaces are separated. (Anay R. Patel et al., 2011)

BUCCAL FORMULATIONS:

- The size of the delivery system varies with the type of formulation, i.e., a buccal tablet may be approximately 5–8mm in diameter, whereas a flexible buccal patch may be as large as 10–15cm2 in area.
- Mucoadhesive buccal patches with a surface area of 1–3 cm2 are most acceptable.
- It has been estimated that the total amount of drug that can be delivered across the buccal mucosa from a 2-cm2 system in 1 day is approximately 10–20 mg.
- The shape of the delivery system may also vary, although for buccal drug administration, an ellipsoid shape appears to be most acceptable.
- The thickness of the delivery device is usually restricted to only a few millimeters.
- The location of the delivery device also needs to be considered
- The maximal duration of buccal drug retention and absorption is approximately 4– 6 h because food and/or liquid intake may require removal of the delivery device.
- Physiology of mucus membrane under disease condition need to be accounted for (e.g.: Cancer patients suffer from oral candidosis)

BUCCAL TABLETS:

Buccal tablets are dry solid dosage forms that may have to be placed in the buccal mucosa. The size of the tablet is restricted to that which can be comfortably retained in place for prolonged periods.

- Buccal adhesive tablets are held between the gum and cheek.
- Generally flat, elliptical or capsule-shaped.

- Troches & lozenges are two other types of tablets used in oral cavity where they are intended to exert a local effect in the mouth or throat.
- Buccoadhesive tablet may be monolithic or bilaminated system.
- Monolithic is multidirectional release
- Bilayered containing core layer & backing layer.
- Backing layer may be of water insoluble material like Ethyl cellulose or hydrogenated castor oil or may be polymeric coating layer
- Backing layer avoids sticking of the tablet to the finger during application. (Pankil A. Gandhi et al., 2011)

Limitations of buccal tablets

- The small surface of contact with mucosa.
- Their lack of physical flexibility.It is difficult to get high release rate, which is required for some drugs.
- The extent and frequency of contact may cause irritation following chronic application of the buccal mucosa. (Pankil A. Gandhi et al., 2011)

BIOADHESIVE POLYMERS:

Bioadhesive polymers have properties to get adhered to the biological membrane and hence capable of prolonging the contact time of the drug with a body tissue. The use of bioadhesive polymers can significantly improve the performance of many drugs. This improvement ranges from better treatment of local pathologies to improved bioavailability and controlled release to enhance patient compliance.

Characteristics of Ideal Bioadhesive Polymers

- It should show bioadhesive properties in both dry and liquid state.
- It should possess an optimum molecular weight to the bioadhesion.
- It should be able to accommodate both oil and water soluble drugs for the

- Purpose of controlled drug delivery.
- It should demonstrate local enzyme inhibition and penetration enhancement properties.
- It should show specificity for attachment to an area or cellular site.
- It should show specificity and stimulate endocytosis.
- It should be inert and compatible with the environment.
- It should be easy and inexpensive to fabricate.
- It should have good mechanical strength.
- It should possess a wide margin of safety both locally and systemically. (Pankil A. Gandhi et al., 2011)

CHAPTER III

LITERATURE REVIEW

CHAPTER III

LITERATURE REVIEW

Sellappan Velmurugan et al., 2013, formulated and evaluated Glipizide mucoadhesive buccal tablets. The tablets were prepared by direct compression technique using different concentrations of mucoadhesive polymers such as Carbopol 940, Sodium Alginate and HPMC K15M in combination. The formulated tablets were evaluated for bioadhesive strength, surface pH, in-vitro drug release. The formulation containing 1:8 ratio of drug and polymer combination showed satisfactory bioadhesion and optimum drug release (72.35±0.04% after 12 hours).

Satyabrata Bhanja et al., 2013, formulated and evaluated the mucoadhesive buccal tablets containing anti diabetic drug, Glimepiride to circumvent the first pass effect and to improve the bioavailability with reduction in dosing frequency and dose related side effects. The tablets were prepared by direct compression method. Six formulations were developed with varying concentrations of polymers like Carbopol 934P, HPMCK4M, and chitosan. The tablets were tested for weight variation, hardness, surface pH, drug content, swelling index, bioadhesive strength, ex-vivo residence time, in-vitro dissolution study, in-vitro drug release kinetic studies, ex-vivo permeation study and stability studies. FTIR studies showed no evidence on interaction between drug, excipients. The best in-vitro drug release profile was achieved with the formulation F3 which contains the drug, carbopol 934P, HPMC K4M and chitosan in the ratio of 1:3.75:8.75:1.25. Finally it was concluded that the best formulation F3 was suitable for all the evaluation parameters and can be permeated through human buccal mucosa.

Patil K C et al., 2013, formulated and evaluated buccoadhesive tablets of Captopril using mucoadhesive polymers. The tablets were prepared by direct compression technique using Carbopol 934P, HPMC K15M and Hydroxy ethyl cellulose as mucoadhesive polymers. Six formulations were developed with varying concentration of polymers. Formulation (F1) containing Carbopol 934P and HPMC K4M in the ratio of (1:2) showed good mucoadhesive strength (18.55) and maximum drug release of 97.66% in 10 hours. Swelling increased with increasing in concentration of Carbopol 934P in tablets. FTIR studies showed no evidence on interaction between drug and polymers. The result indicated that the mucoadhesive buccal tablets of Captopril may be good choice to bypass extensive hepatic first pass metabolism with an increased bioavailability of Captopril.

Ankarao A et al., 2013, formulated and evaluated buccoadhesive bilayer tablets of carvedilol. The tablets were prepared using HPMC K4M, SCMC and Carbopol 934 as bioadhesive polymers to impart mucoadhesion and ethyl cellulose to act as an impermeable backing layer. The mechanism of drug release was found to be non-Fickian diffusion (value of n between 0.5 and 1.0). The study was concluded that mucoadhesive tablets of Carvedilol can be a good way to bypass the extensive hepatic first-pass metabolism and to improve the bioavailability of Carvedilol.

Muthadi Radhika et al., 2013, formulated and evaluated buccoadhesive bilayer tablet of Enalapril Maleate. Tablets of Enalapril Maleate were prepared by direct compression method using bioadhesive polymers like Carbopol 934P, HPMC K15M, HPMC K100M either alone or in combination with backing layer of ethyl cellulose. The maximum bioadhesive strength was observed in tablets formulated with

Carbopol 934P alone. Carbopol 934P and HPMC K100 in the ratio of 1:1.5 could be used to design effective and stable buccoadhesive tablets of Enalapril Maleate.

Muthukumaran M et al., 2013, developed and optimized Hydralazine HCL sustained release mucoadhesive buccal tablets using 2^3 factorial design. The bioadhesive polymers such as Xanthan gum, Carbopol and HPMC were used in combination with ethyl cellulose and magnesium stearate as an impermeable backing layer. The 2^3 full factorial design was employed by selecting the independent three polymer variables at two levels (low and high level). The study was successfully undertook the development of an optimized mucoadhesive and sustained release characteristics. Finally he concluded that mucoadhesive bilayer tablets of Hydralazine HCL could be promising one as they increases bioavailability, minimizes the dose, reduces the side effects and improved patient compliances.

Raviteja Achanta et al., 2013, developed and evaluated buccoadhesive bilayered tablets of Thiocolchicoside. The tablets were prepared using bioadhesive polymers like Carbopol 934P, HPMC by direct compression method. Ethyl cellulose used as an impermeable backing layer which gives unidirectional buccal drug delivery. The results of study revealed that the formulation containing a combination of polymers like Carbopol 934P and HPMC K4M showed suitable in-vitro drug release. These buccoadhesive bilayered tablets were developed to a satisfactory level in terms of drug release, bioadhesive time, physicochemical properties and surface pH.

Gururaj S Kulkarni et al., 2013, developed and evaluated Terbutaline sulphate mucoadhesive buccal tablets. In this study, the attempt was made to prepare mucoadhesive buccal tablets of Terbutaline sulphate with natural polymer sodium

alginate with one side absorption by backing layer with ethyl cellulose. IR spectroscopy did the compatible study between polymers and Terbutaline sulphate and no interaction was found between drug and polymers. All parameters of Terbutaline sulphate buccal tablets were passed the standard of mucoadhesive buccal tablets. It was found that mucoadhesive natural polymers exhibited better adhesiveness and mucoadhesiveness. The in-vitro study of terbutaline sulphate exhibited greater drug release profile with release in the range of 79.25 to 99.85%.

Raviteja Achanta et al., 2012, developed and evaluated buccoadhesive tablets of Losartan Potassium. The buccal route is suitable for drugs, which are susceptible to acid hydrolysis in the stomach or which are extensively metabolized in the liver(first pass metabolism). Losartan Potassium buccoadhesive tablets were prepared by direct compression method using different polymers such as Carbopol 934P, HPMC K4M, HPMC K15LV. In order to increase bioavailability to avoid the hepatic metabolism, the buccal tablets of Losartan Potassium were prepared.

Bhaskar Umaraj et al., 2012, fabricated and evaluated the mucoadhesive buccal tablets of furosemide by wet granulation method using Chitosan, Guar Gum and Hydroxy ethyl cellulose along with Carbopol 934P as mucoadhesive polymers in different ratios. As the amount of polymer in the tablets increases, the drug release rate decreases, whereas swelling index and mucoadhesive strength increases. Ex-vivo residence test for mucoadhesion indicated good mucoadhesive property of the prepared tablets. The formulations containing polymers such as Carbopol 934P:Chitosan and Carbopol 934P:Guar Gum were optimised because of their good mucoadhesive strength.

Appa Rao Potu et al., 2012, formulated and evaluated buccoadhesive Quetiapine Fumarate tablets. The tablets were prepared using HPMC K4M, HPMC K15M and combination of Carbopol and Hydroxy Ethyl Cellulose as mucoadhesive polymers by direct compression method. Sodium deoxycholate was added to formulation to improve the permeation of drug. The formulation were tested for bioadhesion strength, ex-vivo residence time, swelling time and in-vitro dissolution studies. Optimized formulation showed 92% in-vitro release in 8 hours and 67% permeation of drug through porcine buccal mucosa. These findings suggested that buccoadhesive tablets of Quetiapine Fumarate showed significant improvement in oral bioavailability of the drug. FTIR spectra of optimized formulation showed no drug-polymer interaction.

Anand Padole et al., 2012, prepared and evaluated buccal mucoadhesive tablets of lisinopril. The tablets were prepared by direct compression method using different hydrophilic polymers such as hydroxyl propyl methyl cellulose and carbopol. The friability of all the formulations were below 1% which is an indication of good mechanical resistance of tablets. No colour change or no changes in texture were observed when tablets were tested in simulated saliva solution(pH 6.8). The tablet with polymers such as Carbopol 934P:HPMC K4 in the ratio of 2:1 showed maximum swelling index, bioadhesive strength. Novel mucoadhesive buccal tablets of Lisinopril were developed to overcome the first pass metabolism and subsequent low bioavailability of the Lisinopril. The in-vitro studies have shown that this is a potential drug delivery system for Lisinopril with a considerably good stability and release profile.

Vinod Kombath Ravindran et al., 2012, done a project on comparative study of mucoadhesive polymers such as Carbopol 974P and Sodium carboxy methyl cellulose for single unit dosage of Imatinib Mesylate. Gastro retentive mucoadhesive mucoadhesive tablet was prepared by direct compression method using Carbopol 974P and SCMC as mucoadhesive polymers. Drug release profile using the SCMC was preferred to the Carbopol 974P. Hence SCMC can be optimized although Carbopol 974P showed better adhesive nature.

Muthukumaran M et al., 2012, fabricated and evaluated sustained release mucoadhesive bilayer tablets containing Nifedipine. The tablets were prepared by direct compression method using the natural bioadhesive polymers such as Pectin to compare the synthetic polymer such as Carbopol 971P, HPMC K4M and Polyvinyl Pyrrolidine(PVP K30) along with Ethyl Cellulose and Magnesium Stearate as an impermeable backing layer to improve the oral bioavailability. The preformulation was performed by FTIR and DSC. The formulated Nifedipine buccal tablets showed a significant increase in oral bioavailability. Higher bioavailability would be due to avoidance of hepatic first pass metabolism by intestinal lymphatic transport, which circumvents the liver. It was concluded that the dose of Nifedipine buccal tablets needs to be decreased in accordance with increased bioavailability, to minimize its dose related adverse effects.

Ananda Reddy K et al., 2012, formulated and evaluated buccal adhesive tablets of Piroxicam. The tablets were prepared by HPMC K4M and Carbopol 934 as mucoadhesive polymers. The formulations were developed with varying concentrations of polymers such as HPMC K4M and Carbopol 934. The formulation

containing drug:HPMC K4M(in the ratio of 1:3) showed maximum release of drug(97.67% ± 0.41%). FTIR results showed no evidence of interaction between the drug and polymers.

G V Wadageri et al., 2012, developed and evaluated mucoadhesive bilayer buccal tablets of Carvedilol. In this study, an attempt was made to design and evaluate buccoadhesive bilayer tablets of Carvedilol, in order to overcome bioavailability problems, to reduce dose dependent side effects and frequency of administration. Tablets were prepared by direct compression method using combination of polymers(such as HPMC K15M and K4M along with Carbopol 934P and EC as backing layer). The formulation containing HPMC 15CPS(48%W/W), Carbopol 934P(2%W/W of matrix layer) and mannitol was found to be promising. This formulation exhibited an in-vitro drug release of 84.73% in 8 hours along with satisfactory bioadhesion strength(5.17g).

Raghavendra Rao N. G et al., 2012, formulated and evaluated mucoadhesive buccal bilayered lablets of Salbutamol. The tablets were fabricated with objective of avoiding first pass metabolism and prolonging duration of action. The tablets were prepared by direct compression method using the bioadhesive polymers such as Xanthan Gum, Sodium Alginate and Carbopol 934P with Ethyl Cellulose as an impermeable backing layer. The FTIR results revealed that there was no interaction between drug and other excipients. The study concluded that mucoadhesive buccal tablets of Salbutamol can be a good way to bypass the extensive hepatic first pass metabolism and improved the bioavailability.

Suresh kumar P et al., 2011, formulated and evaluated Nebivolol mucoadhesive buccal tablets. The oral controlled release Nebivolol mucoadhesive tablets by using HPMC K4M, HPMC K15M and Carbomer 940 as mucoadhesive polymers were prepared by direct compression method and evaluated for mucoadhesive strength and in-vitro dissolution parameters. This study suggests the polymer HPMC K15M can produce a controlled pattern of drug release in the prepared Nebivolol tablets. The high mucoadhesive strength of this formulation was likely to increase its residence time in the GIT, which eventually improves the extent of bioavailability.

Basawaraj S. Patil et al.,2011, developed and evaluated mucoadhesive buccal tablets of Tizanidine hydrochloride using natural polymer Guar gum. The tablets were prepared by using Guar gum and in combination of Guar gum with Sodium alginate as mucoadhesive polymers. The in-vitro performances were evaluated by drug content uniformity, surface pH, swelling index, mucoadhesive strength and dissolution studies. The swelling index and mucoadhesivity of the tablets were increased with increasing amount of Guar gum and sodium alginate. So it can be concluded that mucoadhesive buccal tablets of Tizanidine hydrochloride can be prepared by using natural polymers avoids first pass metabolism.

Gaurav kumar et al., 2011, fabricated and evaluated flavoured mucoadhesive buccal tablets of Caffeine as CNS stimulantt. Mucoadhesive buccal dosage form of Caffeine anhydrous was designed using a combination of bioadhesive polymers such as Carbopol 934P, HPMC, and SCMC in different ratios. Carbopol 934P showed maximum bioadhesion property. The formulations were tested for their swelling behavior. In which the formulation containing SCMC and Carbopol 934P was found

to be swell to a greater extent than those containing SCMC and HPMC. In-vitro release studies showed that the formulation consisting of 3:1 ratio of SCMC and Carbopol 934P released Caffeine over 8 hours. Caffeine release and bioadhesion of buccal tablets can be controlled by changing the polymer type and concentration.

Ranade A N et al., 2011, developed and evaluated buccal tablets of Quinapril hydrochloride. Quinapril hydrochloride was reported to have low oral bioavailability due to an extensive first pass effect. Buccoadhesive tablets of Quinapril hydrochloride were prepared using mucoadhesive polymers such as Carbopol 974P, HPMC K4M. Citric acid was chosen as permeation enhancer. The tablets were prepared by direct compression technique. DSC studies showed no interaction between drug and excipients. The buccoadhesive tablet of Quinapril hydrochloride was prepared using CP and HPMC provided regulated release upto 3 hours. The presence of penetration enhancer indicated increased penetration of drug across the buccal mucosa which can result in improved bioavailability.

Pankil A Gandhi et al., 2011, done a study on mucoadhesive buccal drug delivery system. The buccal region of oral cavity was found to be an attractive target for administration of the drug of choice, particularly in overcoming deficiency associated with the later mode of administration. Problems such as high first pass metabolism drug degradation in the gastrointestinal environment can be circumvented by administering the drug via the buccal route. Moreover, rapid onset of action can be achieved relative to the oral route and the formulation can be removed if the therapy is required to be discontinued. It is also possible to administer

drugs to patients who unconscious and less co-operative. The buccal mucosa offers several advantages for controlled drug delivery for extended period of time.

Anay R Patel et al., 2011, done a study on mucoadhesive buccal drug delivery system. Within the oral mucosal cavity, the buccal region offers an adorable route of administration for systemic drug delivery. Among the various transmucosal sites available, mucosa of the buccal cavity was found to be the most convenient and easily approachable as retentive dosage forms. sites for the delivery of therapeutic agents for both local and systemic delivery as retentive dosage forms. The mucoadhesive interaction was explained in relation to the structural characteristics of mucosal tissues and the theories and properties of the polymers.

Vijaya Muthumanikandar R et al., 2011, developed and evaluated buccoadhesive tablets of Losartan Potassium. Buccoadhesive tablets were prepared by wet granulation method using the Carbopol 934P, Hydroxy propyl cellulose, Sodium Alginate and SCMC as bioadhesive polymers. The tablets were evaluated for pre and post compression parameters like bioadhesive strength, in-vitro retention time and in-vitro drug release studies. The formulation containing Carbopol and HPC shows higher bioadhesive strength, sustained release of drug and sufficient in-vitro retention time.

Agaiah Goud et al., 2011, formulated and evaluated bioadhesive buccal tablets of Simvastatin. Simvastatin has short biological half life(3 hours), high first pass metabolism and poor oral bioavailability(5%), hence an ideal candidate for buccal delivery system. The tablets were prepared by direct compression technique using Carbopol 934, SCMC and HPMC as mucoadhesive polymers. The formulations were

evaluated for mass variation, hardness, friability, drug content, swelling studies, erosion studies, in-vivo residence time, in-vitro release studies in pH 7.0 phosphate buffer with 0.5% SDS and ex-vivo permeation studies through porcine buccal mucosa. FTIR studies showed no evidence on interaction between drug, polymers and other excipients. The prepared bioadhesive buccal tablets of Simvastatin could help bypass extensive hepatic first pass metabolism and improved bioavailability. The buccal tablets showed that SCMC containing formulations showed better bioadhesion than the HPMC K4M. The drug release rate of formulations prepared with HPMC K4M(max.60.67%) was retarded due to the high viscosity of the polymer and formation of complex matrix network when compared to the low viscosity polymers SCMC(max.78.77%).

Goswami Dhruba Sankar et al., 2011, formulated and evaluated mucoadhesive tablets of Famotidine. The tablets were prepared by conventional wet granulation method employing HPMC K4M, SCMC, Sodium Alginate, Acacia and Tragacanth as mucoadhesive materials to reduce the dosing frequency. The formulations were subjected to different evaluation studies like friability, content uniformity, surface pH. The result showed that formulation containing Famotidine with HPMC K4M and Tragacanth has given better drug release property and better mucoadhesive property.

Lokhande S et al., 2011, formulated and evaluated buccoadhesive tablets of Atenolol. The present study was aimed to formulate the buccoadhesive tablet of Atenolol by adopting Box-Behnken factorial design and using Chitosan, Carbopol 937P and SCMC. The formulations were evaluated for drug content, hardness, thickness, friability, weight variation, in-vitro dissolution study and ex-vivo

bioadhesive strength and time. The ex-vivo bioadhesion studies formulations on sheep buccal mucosa showed better bioadhesion with high bioadhesion time. In-vitro drug release studies indicated that the drug release was higher and controlled when the polymer content(Carbopol 937P and Chitosan) was 100mg per tablet. The release of Atenolol was controlled by the diffusion from the matrix formed by the polymers. Oral controlled release bioadhesive tablets of Atenolol were formulated as an approach to avoid fluctuations in plasma drug concentration and thereby to improve its bioavailability.

Amit Alexander et al., 2011, done a study on polymers and permeation enhancers as a specialized components of mucoadhesives. Mucoadhesive polymers recently gained interest among pharmaceutical scientists as a means of improving drug delivery by promoting dosage form residence time and contact time with the mucous membranes. Pharmaceutical aspects of mucoadhesion have been the subject of great interest during recent years because mucoadhesion could be a solution for bioavailability problems.

Santanu Roychowdhury et al., 2011, done a study on buccal mucoadhesive drug delivery systems. Buccal mucosa is the preferred site for both systemic and local drug action. The mucosa has a rich blood supply it relatively permeable. In this article the advantages and limitations related to the buccal drug delivery has also been discussed. In buccal drug delivery systems mucoadhesion is the key element so various mucoadhesive polymers have been utilized in different dosage form. Various mucoadhesive dosage forms such as Chewing gum, Patches, Tablets, Hydrogel, Thiolated tablets are discussed in this review article. Finally he concluded that

buccal region provides a convenient route for both local and systemic drug actions. Buccal adhesive systems offer innumerable advantages in term of accessibility, administration and withdrawal, retentivity, low enzyme activity, economy and high patients compliance. The future direction of buccal adhesive drug delivery lies in vaccine formulations and delivery of small proteins/peptides.

Yadav Deepak R et al., 2011, developed and evaluated buccoadhesive Metoclopramide Hydrochloride tablet formulations. Tablets were fabricated by direct compression method with objective of avoiding extensive first pass metabolism and to prolong its duration of action with reduction in dosing frequency. The mucoadhesive polymers used in the formulations were Carbopol 934P, Chitosan, HPMC K4M and HPMC K15M. Formulation (F4) containing Carbopol 934P and HPMC K4M in the ratio of 1:1 showed good mucoadhesive force and maximum drug release of 96.10% in 10 hours. He concluded that mucoadhesive buccal tablets of Metoclopramide may be a good way to bypass the extensive hepatic first-pass metabolism and to improve the bioavailability of Metoclopramide.

Jitendra kumar P et al., 2011, formulated and evaluated buccoadhesive bilayered tablets of Carvedilol. The tablets were prepared using HPMC K4M, CMC Sodium, Carbopol 934 as bioadhesive polymers to impart mucoadhesion and ethyl cellulose to act as an impermeable backing layer. Buccal tablets were evaluated by different parameters such as weight uniformity, content uniformity, thickness, hardness, surface pH, swelling index, mucoadhesive strength, drug release and in-vitro drug permeation. The mechanism of drug release was found to be non-Fickian diffusion (value of n between 0.5 and 1.0) for both the buccal tablets (F2 and F5). Finally he

concluded that mucoadhesive buccal tablets of Carvedilol may be a good way to bypass the extensive hepatic first-pass metabolism and to improve the bioavailability of Carvedilol through buccal mucosa.

Gaurav Kumar et al., 2011, fabricated and evaluated flavoured mucoadhesive buccal tablet of caffeine as CNS stimulant. In this study, a bioadhesive dosage form of caffeine anhydrous was designed using a combination of bioadhesive polymers(sodium carboxymethyl cellulose, Carbopol 934P and Hydroxy propyl methyl cellulose) in different ratios. Carbopol 934P showed maximum bioadhesion. The formulations were tested for their testing behavior using the agar gel plate method in which formulations containing sodium carboxymethyl cellulose and Carbopol was found to swell to a greater extent than those containing sodium carboxymethyl cellulose ang Hydroxy propylmethyl cellulose. In-vitro release studies showed that the formulation consisting of 3:1 ratio of sodium carboxymethyl cellulose and Carbopol 934P released Caffeine over 8 hours. Finally it was concluded that this noval formulations can reduce the need of frequent administration and enhanced patient compliance with better absorption through buccal route.

Shivanand K et al., 2010, fabricated and evaluated Mucoadhesive bilayered buccal tablets of Tizanidine Hydrochloride, using mucoadhesive polymers Carbopol 934P, HPMC K4M, HPMC K15M and Sodium carboxymethyl cellulose along with ethyl cellulose as an impermeable backing layer. The preformulation studies of TZD HCL like compatibility studies with polymers, using FTIR and DSC were carried out. The tablets were evaluated for weight variation, hardness, thickness, surface pH, mucoadhesive strength, mucoadhesive time, swelling index, in-vitro drug release

studies and ex-vivo permeation. He concluded that CArbopol 934P was more hydrophilic than HPMC, so it could swell rapidly. Therefore decrease of Carbopol content delayes the drug release.drug release rate was increased with increasing amount of hydrophilic polymer.

Ravi Krishna V et al., 2010, formulated and evaluated buccoadhesive tablets of Furosemide. The tablets of Furosemide were prepared by direct compression method using bioadhesive polymers like Carbopol 941NF, 971P, Methocel K4M, Methocel K15M and combination of SCMC, Carbopol 971P in different ratios with backing layer of Cyanoacrylate adhesive tape. Buccal tablets were evaluated by different methods for parameters such thickness, hardness, weight uniformity, swelling index, surface pH, ex-vivo bioadhesion strength, ex-vivo residence time, in-vitro drug release, in-vitro drug release, ex-vivo drug permeation, stability studies, in-vivo mucoadhesive performance studies. Bioadhesion strength was increased with increase in the concentration of Carbopol. The buccal adhesive tablets of Furosemide were found to be good choice to bypass the first pass metabolism.

Guda Aditya et al., 2010, designed and evaluated controlled release mucoadhesive buccal tablets of Lisinopril. Tablets were prepared by direct compression method using various polymers such as Carbopol 934, HPMC, Hydroxy Ethyl Cellulose as mucoadhesive polymers. The tablets were evaluated for hardness, wait variation, thickness, percentage of drug content, surface pH, in-vitro studies like swelling, mucoadhesive strength. The formulation containing Carbopol 934 and HPMC K4M in the ratio of 2:4 showed good mucoadhesive strength(36.4) and maximum drug release of 97.1% in 10 hours. So, the mucoadhesive buccal tablet of Lisinopril may

be a good choice to bypass the extensive hepatic first pass metabolism with an improvement in the bioavailability of Lisinopril through buccal mucosa.

Punitha S et al., 2010, done a study on polymers in mucoadhesive buccal drug delivery system. Among the various transmucosal sites available, mucosa of the buccal cavity was found to be the most convenient and easily accessible site for the delivery of therapeutic agents for local and systemic delivery as retentive dosage forms. The success and degree of mucoadhesion bonding was influenced by various polymer based properties. Buccal adhesive system offered innumerableadvantages in terms of accessibility, administration and withdrawal, retentivity, low enzymatic activity, economy and high patient compliance.

Bhanja Satyabrata et al., 2010, designed and evaluated mucoadhesive buccal tablets of perindopril by sintering technique to avoid the first pass metabolism and to improve its bioavailability with reduction in dose and also dose related side effects. The tablets were prepared by direct compression method containing polymer Poly ethylene oxide and Carnauba Wax. The prepared tablets were sintered at various temperature like 60^0C and 70^0C for 1.5 hours and 3 hours. The best in-vitro drug release profile was achieved with formulation(sintered at 60^0C for 1.5 hours) containing drug, Polyethylene Oxide and Carnauba Wax in the ratio of 1:15:10. So mucoadhesive buccal tablets of perindopril prepared by sintering technique may be good approach to bypass the extensive first pass metabolism, to improve the bioavailability to prolong the duration of action.

Satyabrata Bhanja et al., 2010, formulated and evaluated mucoadhesive buccal tablets of Timolol maleate to circumvent the first pass effect and to improve its

bioavailability with reduction in dosing frequency and dose related side effects. The tablets were prepared by direct compression with varying concentration of polymers like Carbopol 934, Poly ethylene oxide and HPMC. FTIR studies showed no evidence on interactions between drug, polymers and excipients. The best in-vitro drug release profile was achieved with the formulation which contains the drug, Carbopol 934P and HPMC K4M in the ratio of 1:2.5:10. It can be seen that by increasing the concentration of Carbopol 934P in the formulation, the drug release rate from the tablets was found to be decreased. But when the concentration of HPMC K4M increased, the drug release rate was found to be increased.

Hiremath J G et al., 2009, prepared and characterized Simvastatin loaded mucoadhesive bilayered tablets. The purpose of this research work was to prepare the buccoadhesive bilayered tablet of Simvastatin for the treatment of hypercholesterolemia, by using the buccoadhesive polymers such as Carbopol(CP), HPMC and PVP in different concentration. Ethyl Cellulose was used in backing layer because of its water impermeable nature. Tablets were prepared by direct compression method. Tablets were subjected for physicochemical characterization tests such as FTIR, DSC, hardness, weight variation, friability, mucoadhesive strength, in-vitro drug release study, in-vitro permeation and stability in human saliva. The FTIR and DSC analysis of drug, polymers, physical mixtures and formulation indicated that the compatibility of drug with the excipients. The study was concluded that mucoadhesive buccal devices of Simvastatin can be a good way to bypass the extensive hepatic first pass metabolism and to improve the bioavailability of Simvastatin.

Deelip Derle et al., 2009, formulated and evaluated bioadhesive Bi-layered tablet of Propranolol Hydrochloride using the bioadhesive polymers such as Sodium Alginate and Carbopol 971P along with Ethyl Cellulose as a impermeable backing layer. The tablets were Sodium Alginate and Carbopol 971P in the ratio of 5:1 showed the maximum percentage of in-vitro drug release without disintegration in 12 hours. The mechanism of drug release was found to be zero order kinetics. The mucoadhesive buccal tablets of Propranolol hydrochloride can help to bypass extensive hepatic first pass metabolism and hence improve bioavailability.

Margret Chandira R et al., 2009, designed and developed controlled release mucoadhesive oral tablet of Clarithromycin. He formulated the tablets using four mucoadhesive polymers namely Carbopol 974P, HPMC K4M and HPMC K15M. Formulations F9 and F12 were formulated by using polymers, HPMC K4M, HPMC K15M and Carbopol provided controlled release of Clarithromycin over the period of 12 hours. Tablets of batch F9 and F12 were selected as an optimum batch and evaluated for further parameters like accelerated stability study and characterization using IR spectroscopy. The stability study revealed that there was no significant change in dissolution profile and mucoadhesive strength for a period of one month.

Manivannan R et al., 2008, formulated and evaluated mucoadhesive buccal tablets of Diltiazem Hydrochloride. The tablets were prepared using Carbopol 934, SCMC, HPMC, Sodium Alginate and Guar Gum as mucoadhesive polymers. The Carbopol 934 was used as a primary polymer because of its excellent mucoadhesive property and secondary polymers like HPMC, SCMC, Sodium Alginate and Guar Gum were used. The formulations were tested for in-vitro drug release and in-vitro swelling

studies. Formulation with drug:Carbopol(in the ratio of 1:4) showed maximum release of 76.98% in 8 hours and swelling index of 3.7 after 8 hours. Formulations followed zero order drug release. FTIR showed no evidence on interaction between drug and polymers.

Ganesh P et al., 2008, developed and evaluated mucoadhesive buccal tablets of Domperidone. The tablets were prepared fabricated with objective of avoiding first pass metabolism and to improve its bioavailability with reduction in dosing frequency. The mucoadhesive polymers used in the formulations were Carbopol 934P, Methocel K4M, Methocel E15LV and Chitosan. Tablets were prepared by direct compression method using polymers in different ratios. The formulations were characterized for swelling index, in-vitro bioadhesion strength and in-vitro release studies. The best mucoadhesive performance and in-vitro drug release profile were exhibited by the tablet containing Chitosan and Methocel K4M in ratio of 1:1. It was observed that the optimized formulation followed Hixson Crowel release kinetics.

Johnson. P et al., 2005, done a project on the use of mucoadhesive polymers in buccal drug delivery. Buccal delivery involves the administration of the desired drug through the buccal mucosal membrane lining of the oral cavity. Unlike oral drug delivery, which presents a hostile environment for drugs, especially proteins and polypeptides, due to acid hydrolysis and the hepatic first pass metabolism, the mucosal lining of buccal tissues provides much milder environment for drug absorption. Starting with a review of the oral mucosa, mechanism of drug permeation, and characteristics of the desired polymers, this article then proceeds to

cover the theories behind the adhesion of bioadhesive polymers to the mucosal epithelium.

Yasuko Obata et al., 2002, done a project on buccal absorption of Ergotamine tartrate using the bioadhesive tablet system in guinea pigs. The tablets were prepared by direct compression method using Carboxy vinyl polymers and Hydroxy propyl cellulose(1%W/W) as a mucoadhesive polymers. Buccal tablet showed better absorption of Ergotamine Tartrate compared with Polyvinyl alcohol gel in Guinea pig.

CHAPTER IV

AIM OF THEWORK

CHAPTER IV

AIM OF THE WORK

Nowadays, tablet dosage forms are supplanted by new drug delivery system because of problems like hepatic metabolism, GI toxicity which leads to non-compliance and ineffective therapy. This problem can be overcome by formulating the drug in to buccal adhesive tablets for mucosal absorption with reduced GI toxicity, hepatic first pass metabolism and improved bioavailability. Moreover, rapid onset of action can be achieved relative to the oral route. The main mechanism behind buccal mucoadhesion is the formation of an intimate contact between the dosage form and the absorptive buccal mucosa. Buccal adhesive formulations are mainly supported by mucoadhesive polymers as the adhesive component.

Olmesartan medoxomil is a angiotensin receptor II antagonist used alone or with other antihypertensive agent. Olmesartan medoxomil is the most recent member of angiotensin receptor blocker which is chemically, (5-methyl-2-oxo-2H-1, 3-dioxol-4-yl) methyl 4-(2-hydroxypropan-2-yl)-2-propyl-1 - ({4- [2-(2H-1, 2, 3, 4-tetrazol-5-phenyl] phenyl} methyl)-1H-imidazole-5-carboxylate.

Olmesartan medoxomil is practically insoluble in water, freely soluble in organic solvents. It is a novel antihypertensive agent administered orally with absolute bioavailability of about 26% due to extensive hepatic first pass metabolism.

The main aim of this study is to formulate and evaluate buccal adhesive tablets of olmesartan medoxomil using varios mucoadhesive polymers such as carbopol 934P, HPMC K15M, sodium carboxymethyl cellulose, chitosan and xanthan gum for reducing its hepatic first pass metabolism, dose reduction and controlled release of drug with improved bioavailability and also to target the drug at its specific site of absorption (buccal mucosa).

CHAPTER V

PLAN OF WORK

CHAPTER V

PLAN OF WORK

1. PREPARATION OF STANDARD CALIBRATION CURVE OF OLMESARTAN MEDOXOMIL

(a) Preparation of phosphate buffer pH 6.8

(b) Determination of λ_{max} of olmesartan medoxomil

(c) Preparation of calibration curve of olmesartan medoxomil

2. PREFORMULATION (COMPATABILITY) STUDIES

(a) Fourier transform infrared spectroscopic studies (FTIR)

3. FORMULATION OF OLMESARTAN MEDOXOMIL BUCCAL ADHESIVE TABLETS

Preparation of buccal adhesive tablets of olmesartan medoxomil using different concentrations of hydrophilic swellable gel forming polymers (carbopol 934P, HPMC K15M, sodium carboxy methyl cellulose, chitosan, xanthan gum) by using direct compression technique.

4. EVALUATION OF OLMESARTAN MEDOXOMIL BUCCAL ADHESIVE TABLET

I. Pre compressional evaluation of powder blend

(a) Bulk density (gm/ml)

(b) Tapped density (gm/ml)

(c) Compressibility (or) Carr's Index

(d) Hausner's ratio

(e) Angle of repose (θ)

(f) Drug content of powder blend

II. Post compressional evaluation of buccal adhesive tablet

(a) General appearance

(b)Tablet dimension

(c) Hardness test

(d) Friability test

(e) Weight variation test

(f) Estimation of drug content for tablets

(g) Determination surface pH

(h) *Ex-vivo* mucoadhesive strength

(i) Swelling index studies

(j) *In vitro* release studies

(k*) In vitro* drug release kinetics studies

5. SELECTION AND EVALUATION OF BEST FORMULATION

(a) Infrared spectroscopic studies (IR)

(b) Differential scanning calorimetric studies (DSC)

(c) Stability studies

CHAPTER VI

MATERIALS AND EQUIPMENTS

CHAPTER VI

FORMULATION AND EVALUATION OF MUCOADHESIVE BUCCAL TABLETS OF OLMESARTAN MEDOXOMIL

MATERIALS:

MATERIAL NAME	SUPPLIERS
Olmesartan Medoxomil	Gift sample from Medopharm (P) Ltd, Chennai.
Carbopol 934	SD Fine Chemicals, Mumbai.
HPMC K15M	Steril-gene Life Sciences (P) Ltd, Pondicherry.
Xanthan Gum	Steril-gene Life Sciences (P) Ltd, Pondicherry.
Sodium carboxy methyl cellulose	Steril-gene Life Sciences (P) Ltd, Pondicherry.
Chitosan	HiMedia Laboratories (P) Ltd, Mumbai.
Lactose	Steril-gene Life Sciences (P) Ltd, Pondicherry.
Mannitol	Steril-gene Life Sciences (P) Ltd, Pondicherry.
Magnesium stearate	Universal Scientific Appliances, Madurai, India.
Talc	Universal Scientific Appliances, Madurai, India.
Methanol	Universal Scientific Appliances, Madurai, India
Sodium Hydroxide	High Purity Laboratory Chemicals (P) Ltd.

EQUIPMENTS

NAME	MANUFACTURER
Electronic Weighing Balance	A & D Company HR 200, Japan
Single Punch Tablet Compression Machine	Cadmach Machinery Co. Pvt. Ltd, Ahmadabad.
UV Visible Spectrophotometer	UV-1700 Pharmaspec, Shimadzu, Japan.
Digital Tablet Dissolution Test Apparatus	Disso 2000, Lab India, Mumbai.
Friability Test Apparatus	Indian Equipment Corporation, Mumbai.
Vernier Caliper	Linker, Mumbai.
Tablets hardness tester(Monsanto)	Praveen Enterprises, Bangalore.
Fourier Transform Infrared Spectroscopy	Shimadzu , Japan
Modified Physical Balance	ASIA Scientific Company, India.
Differential Scanning Calorimeter	DSC Q 200, Mumbai

CHAPTER VII

DRUG PROFILE

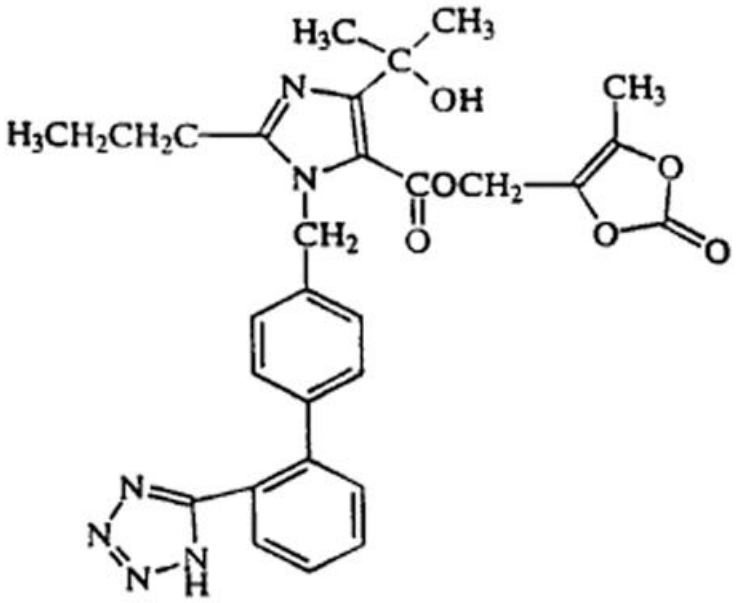
CHAPTER VII

DRUG PROFILE

DRUG NAME : OLMESARTAN

SYNONYM : Olmesartan medoxomil

STRUCTURE:



FORMULA : $C_{24}H_{26}N6O_3$

MOLECULAR WEIGHT : 446.5

SYSTEMATIC IUPAC NAME : 4-(2-hydroxypropan-2-yl)-2-propyl-1-({4-[2-(1H-1,2,3,4-tetrazol-5-yl-)phenyl] phenyl} methyl)-1H-imidazole-5-carboxylic acid

APPEARANCE : White to pale yellowish powder

SOLUBILITY	**:**	Practically insoluble in water, sparingly soluble in methanol
MELTING POINT	**:**	175-180º c
PKa	**:**	4.3
PARTITION COEFFICIENT	**:**	Log P 2.14
HALF LIFE	**:**	Approximately 13 hours
ROUTE OF ADMINISTRATION	**:**	Oral
DOSE	**:**	5mg, 20 mg 40 mg
DOSAGE FORM	**:**	Tablets 5mg, 20mg 40 mg
USE	**:**	Antihypertensive

PHARMACOLOGY:

Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the rennin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation and renal reabsorption of sodium. Olmesartan blocks the vasoconstrictor effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor in vascular smooth muscle. Its action is therefore independent of the pathways for angiotensin II synthesis. Olmesartan has more than a 12, 500-fold greater affinity for the AT_1 receptor than for the AT_2 receptor.

PHARMACODYNAMICS:

Olmesartan, a specific angiotensin II type I antagonist is used alone or with other antihypertensive agents to treat hypertensive agents to treat hypertension. Unlike the angiotensin receptor antagonist losartan, Olmesartan does not have an active metabolite or possess uricosuric effects. Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on rennin secretion, but the resulting increased plasma rennin activity and circulating angiotensin II levels do not overcome the effect of Olmesartan on blood pressure.

PHARMACOKINETICS:

Olmesartan medoxomil is an ester prodrug that is hydrolysed during absorption from the gastrointestinal tract to the active form Olmesartan. The absolute bioavailability is about 26%. Peak plasma concentrations of Olmesartan occur about 1 to 2 hours after oral doses. Olmesartan is at least 99% bound to plasma proteins. It is excreted in the urine and the bile as olmesartan; about 35 to 50% of the absorbed dose is excreted in the urine and the remainder in the bile. The terminal elimination half-life is between 10 and 15 hours.

Distribution:

The volume of distribution of Olmesartan is approximately 17 L. Olmesartan is highly bound to plasma proteins (99%) and does not penetrate red blood cells**.** The protein binding is constant at plasma Olmesartan concentrations well above the range achieved with recommended doses.

Metabolism and Excretion:

Following the rapid and complete conversion of Olmesartan medoxomil to Olmesartan during absorption, there is virtually no further metabolism of Olmesartan. Total plasma clearance of Olmesartan is 1.3 L/h with a renal clearance of 0.6 L/h.

Approximately 35% to 50% of the absorbed dose is recovered in urine while the remainder is eliminated in feces via the bile.

ADVERSE EFFECTS:

Dizziness, headache dose-related orthostatic hypotension.

CONTRAINDICATIONS:

Contraindicated in pregnant or intended to be pregnant and lactating mothers.

DRUG INTERACTIONS:

Drug-Drug Interactions:

Drospirenone

Increased risk of hyperkalemia.

Tobramycin

Increased risk of nephrotoxicity.

Trandolapril

May increase the adverse effects of Trandolapril.

Trepostinil

Additive hypotensive effect.

Diuretics:

Patients on diuretics, and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction in blood pressure after initiation of therapy with olmesartan. The possibility of symptomatic hypotension with the use of olmesartan can be minimized by discontinuing the diuretic prior to initiation of treatment. No drug interaction of clinical significance has been identified with thiazide diuretics.

Agents Increasing Serum Potassium:

Since olmesartan decreases the production of aldosterone, potassium-sparing diuretics or potassium supplements should be given only for documented hypokalemia and with frequent monitoring of serum potassium. Potassium-containing salt substitutes should also be used with caution.

Pravastatin:

Olmesartan decreased the Cmax and AUC of pravastatin by approximately 25% and 21% respectively. Since there is a high degree of variability in the bioavailability of pravastatin, this finding is not considered to be clinically relevant.

Warfarin:

There was no effect on either the pharmacokinetics or pharmacodynamics of warfarin when coadministered with Olmesartan medoxomil) in healthy volunteers.

Digoxin:

No pharmacokinetics or pharmacodynamics effects were reported when olmesartan was co-administered with digoxin in healthy volunteers.

Antacids:

The bioavailability of Olmesartan was not significantly altered when co-administered with antacids.

Cytochrome P450 Enzyme Systems:

Unlike some other angiotensin II receptor blockers, Olmesartan medoxomil is not metabolized by cytochrome P450 enzymes. Interactions with drugs that inhibit, induce or are metabolized by these enzymes are not expected.

Lithium salts:

As with other drugs which eliminate sodium, lithium clearance may be reduced in the presence of Olmesartan. Therefore, serum lithium levels should be monitored carefully if lithium salts are to be administered with Olmesartan medoxomil. Lithium generally should not be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity.

NSAID Agents including Selective Cyclooxygenase-2 Inhibitors(COX-2 Inhibitors):

In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration of NSAIDs, including selective COX-2 inhibitors, with angiotensin II receptor

antagonists, including Olmesartan, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Renal function should be monitored periodically in patients receiving Olmesartan and NSAID therapy.

The antihypertensive effect of angiotensin II receptor antagonists, including Olmesartan may be attenuated by NSAIDs including selective COX-2 inhibitors.

Drug-Food Interactions:

Olmesartan may be administered with or without food as it does not affect the bioavailability.

TOXICITY:

Symptoms of overdose include dehydration, dry mouth, excessive thirst, muscle pain or cramps, nausea and vomiting, weakness, dizziness, low blood pressure and slow or irregular heartbeat.

STORAGE AND STABILITY:

15-30ºC

(www.drugbank.com)

(www.usfda.com)

CHAPTER VIII

EXCIPIENTS PROFILE

CHAPTER VIII

EXCIPIENTS PROFILE

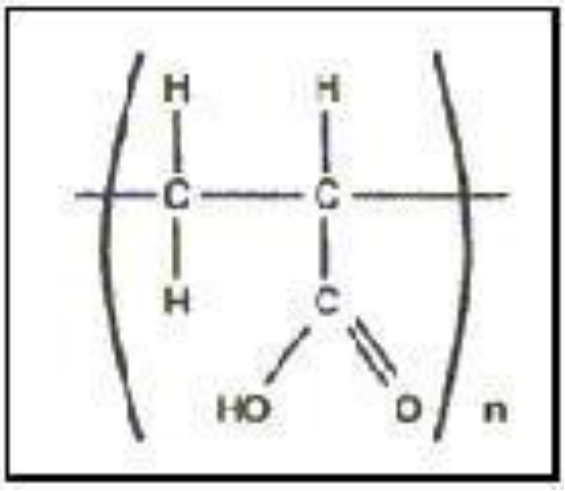
CARBOPOL 934

Carbopol 934P is cross-linked with allyl sucrose and is polymerized in solvent benzene.

SYNONYMS:

Acritamer acrylic acid polymer; Carbopol; carboxypolymethylene, polyacrylic acid; carboxyvinyl polymer; Pemulen; Ultrez.

STRUCTURE:



EMPIRICAL FORMULA AND MOLECULAR WEIGHT:

Carbomers are synthetic high-molecular-weight polymers of acrylic acid that are crosslinked with either allyl sucrose or allyl ethers of pentaerythritol. They contain between 56% and 68% of carboxylic acid (COOH) groups 104 400 g/mol for Carbopol 940 have been reported.

STRUCTURAL FORMULA:

Carbomer polymers are formed from repeating units of acrylic acid. The monomer unit is shown above. The polymer chains are crosslinked with allyl sucrose or allylpentaerythritol.

FUNCTIONAL CATEGORY:

Bioadhesive; emulsifying agent; release-modifying agent; suspending agent; tablet binder; viscosity-increasing agent.

APPLICATIONS IN PHARMACEUTICAL FORMULATION OR TECHNOLOGY:

- Carbomers are mainly used in liquid or semisolid pharmaceutical formulations as suspending or viscosity-increasing agents.
- Formulations include creams, gels, and ointments for use in ophthalmic, rectal, and topical preparations.
- Controlled release in tablets.
- Bioadhesion in buccal, ophthalmic, intestinal, nasal, vaginal and rectal applications.
- Thickening at very low concentration to produce a wide range of viscosities and flow properties in topical, lotions, creams and gels.
- Permanent suspensions of insoluble ingredients in oral suspensions and topical.

Emulsifying agent	**:**	0.1–0.5
Gelling agent	**:**	0.5–2.0
Suspending agent	**:**	0.5–1.0
Tablet binder	**:**	5.0–10.0
Description	**:**	Carbomers are white-colored, ‘fluffy’, acidic, hygroscopic powders with a slight characteristic odor.
Pharmacopeial Specifications	**:**	Carbomer 940 (0.5 w/v) — 40000–60000(a)

TYPICAL PROPERTIES:

- **Acidity/alkalinity**
- pH = 2.7–3.5 for a 0.5% w/v aqueous dispersion;
- pH = 2.5–3.0 for a 1% w/v aqueous dispersion.

Bulk Density	**:**	1.76–2.08 g/cm3
Tapped Density	**:**	1.4 g/cm3
Glass transition temperature	**:**	100–105 ^{o}C
Melting point	**:**	Decomposition occurs within 30 minutes at 260^{o}C.

Moisture content:

Normal water content is up to 2% w/w. However, carbomers are hygroscopic and a typical equilibrium moisture content at 258C and 50% relative humidityis 8–10% w/w. The moisture content of a carbomer does not affect its thickening efficiency. (Hand book of Pharmaceutical Excipients by Raymond C. Rowe et .al., 2009)

CHITOSAN

Chitosan is the term applied to deacetylated chitins in various stages of deacetylation and depolarization and it is therefore not easily defined in terms of its exact chemical composition. Partial deacetylation of chitin results in the production of chitosan which is a polysaccharide comprising copolymers of glucosamine and n-acetylglucosamine.

MOLECULAR WEIGHT:

Chitosan is commercially available in several types and grades that vary in molecular weight between 10,000 and 1,000,000 and vary in degree of acetylation and viscosity.

SYNONYMS:

2-amino-2 –deoxy-(1,4)-ß-d-glucopyranan; deacetylated chitin; deacetyl chitin; ß-1,4- amino 2-deoxy-d-glucopyranosamine

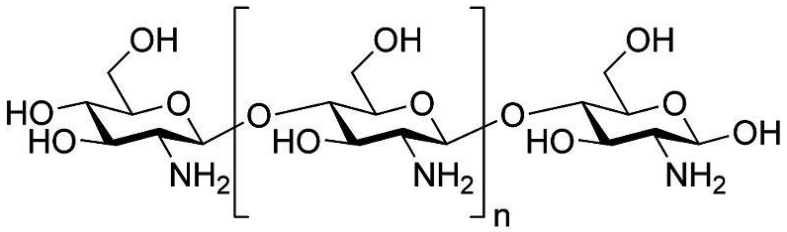
CHEMICAL NAME:

poly-ß-(1,4)-2-amino-2-deoxy-d-glucose

DESCRIPTION:

chitosan occurs as odorless,white or creamy whitepowder or flakes.fibre formation is quite common during precipitation and the chitosan may look ‘cotton like’.

STRUCTURAL FORMULA:



FUNCTIONAL CATEGORY:

Coating agent, disintegrant; film forming agent; mucoadhesive; tablet binder; viscosity-increasing agent

TYPICAL PROPERTIES:

Acidity:

PH 4.0-6.0(1%w/v aqeous solution)

Density:

1.35-1.40 g/cm3

Glass transition temperature:

203^{o}C

MOISTURE CONTENT:

Chitosan absorbs moisture from the atmosphere ,the amount of water absorbed depending upon the initial moisture content and the temperature and relative humidity of surrounding air.

PARTICLE SIZE DISTRIBUTION:

<30 mm

SOLUBILITY:

Sparingly soluble in water, practically, insoluble in ethanol95% and other organic solvents and neutral or alkali solutions at pH above 6.5.

INCOMPATIBILITY:

Chitosan is incompatible with strong oxidizing agents.

SAFETY:

Chitosan is investigated widely for use as an excipient in oral and other pharmaceutical formulation. It is biocompatible with both healthy and infected skin.chitosan has been shown to be biodegradable.

STABILITY AND STORAGE CONDITIONS:

Chitosan powder is a stable material at room temperature, although it is hygroscopic after drying. Chitosan should be stored in tightly closed comtainer in a cool, dry place and it should be stored at a temperature of 2-80c

APPLICATIONS IN PHARMACEUTICAL FORMULATION:

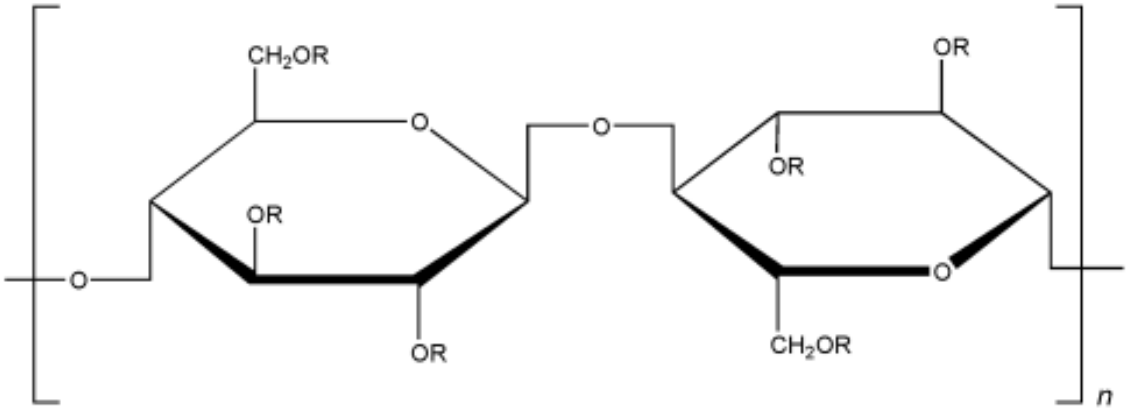
The suitability and performance of chitosan as a component of pharmaceutical formulations for drug delivery applications has been investigated in numerous studies. These include controlled drug delivery applications, used as a component of mucoadhesive dosage forms, rapid release dosage forms, improved peptide delivery.chitosan has been processed in to several pharmaceutical dosage forms, including gels, films, beads, microspheres, tablets and coating of liposomes. (Raymond *et al.*, 2006).

HYDROXY PROPYL METHYL CELLULOSE

SYNONYM:

- Hypromellose.
- Methocel

STRUCTURE:(Hand book of Pharmaceutical Excipients. Pharmaceutical Press, London. 5th edtition)



where R is H, CH3, or CH3CH(OH)CH2

EMPIRICAL FORMULA:

It is a partly O-methylated and O-(2-hydroxypropylated) cellulose. It is available in several grades that vary in viscosity and extent of substitution.

MOLECULAR WEIGHT:

10 000–1 500 000 Dalton

DESCRIPTION:

- **Colour**: white or creamy-white fibrous or granular powder.
- **Odour**: odourless.
- **Taste**: Tasteless.

Solubility:

Soluble in cold water, forming a viscous colloidal solution; practically insoluble in hot water, chloroform, ethanol (95%), and ether, but soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane, and mixtures of water and alcohol. Certain grades of hypromellose are soluble in aqueous acetone solutions, mixtures of dichloromethane and propan-2-ol, and other organic solvents. Some grades are swellable in ethanol.

Density (bulk): 0.341 g/cm^3

Density (tapped): 0.557 g/cm^3

Density (true):1.326 g/cm^3

Melting point: Browns at 190–2008°C; chars at 225–2308°C

Glass transition temperature: 170–1808°C.

METHOD OF MANUFACTURE:

A purified form of cellulose, obtained from cotton linters or wood pulp, is reacted with sodium hydroxide solution to produce a swollen alkali cellulose that is chemically more reactive thanuntreated cellulose. The alkali cellulose is then treated with chloromethane and propylene oxide to produce methyl hydroxypropyl ethers of cellulose. The fibrous reaction product is then purified and ground to a fine, uniform powder or granules. Hypromellose can then be exposed to anhydrous hydrogen chloride to induce depolymerization, thus producing low viscosity grades.

Typical viscosity values for 2 % (w/v) aqueous solutions of different viscosity grades of hpmc at 20°c:

Methocel K100 Premium LVEP : 100

Methocel K4M Premium : 4000

Methocel K15M Premium : 15000

Methocel K100M Premium : 100 000

Methocel E4M Premium : 4000

Methocel F50 Premium : 50

Methocel E10M Premium CR : 10 000

Methocel E3 Premium LV : 3

Methocel E5 Premium LV : 5

Methocel E6 Premium LV : 6

Methocel E15 Premium LV : 15

Methocel E50 Premium LV : 50

Metolose 60SH : 50, 4000, 10 000

Metolose 65SH : 50, 400, 1500, 4000

Metolose 90SH : 100, 400, 4000, 15 000

STORAGE CONDITION:

It should be stored in a well-closed container, in a cool, dry place.

HANDLING PRECAUTION:

- Hypromellose dust may be irritant to the eyes and eye protection is recommended.
- Excessive dust generation should be avoided to minimize the risks of explosion. Hypromellose is combustible.

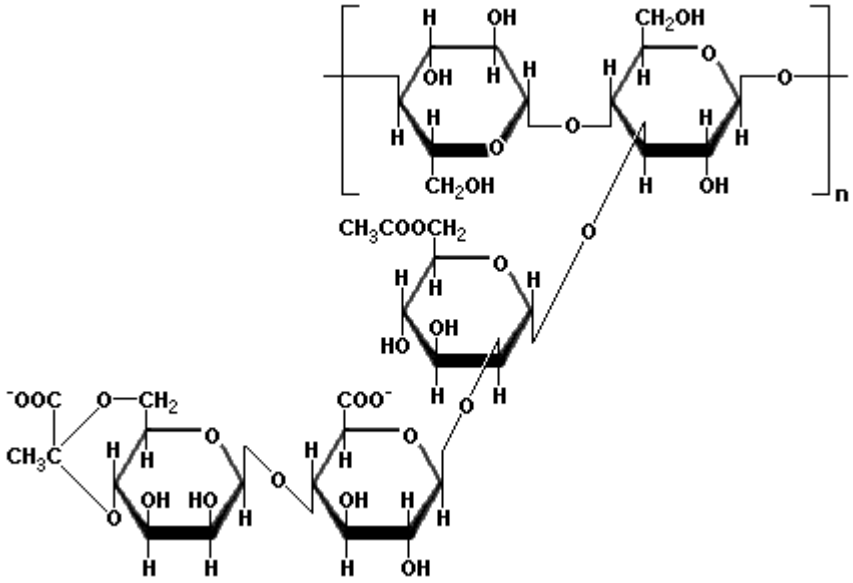
(Hand book of Pharmaceutical Excipients by Raymond C. Rowe et.al., 2009)

XANTHAN GUM

SYNONYMS:

- Corn sugar gum.
- Keltrol.
- Rhodigel.
- Vanzan NF.
- Xantural.

STRUCTURE: (Hand book of Pharmaceutical Excipients. Pharmaceutical Press, London. 5thedtition)



EMPIRICAL FORMULA:

$(C_{35}H_{49}O_{29})$ n

MOLECULAR WEIGHT:

2 x10^6

DESCRIPTION:

Colour: White free flowing fine powder.

Odour :Oduorless.

Taste :Tasteless.

Melting point:

Chars at 270°C.

Solubility:

- Practically insoluble in ethanol and ether;
- Soluble in cold or warm water.

Functional Category:

- Stabilizing agent.
- Suspending agent.
- Viscosity-increasing agent

Storage Conditions:

It should be stored in a well-closed container.

Handling Precautions:

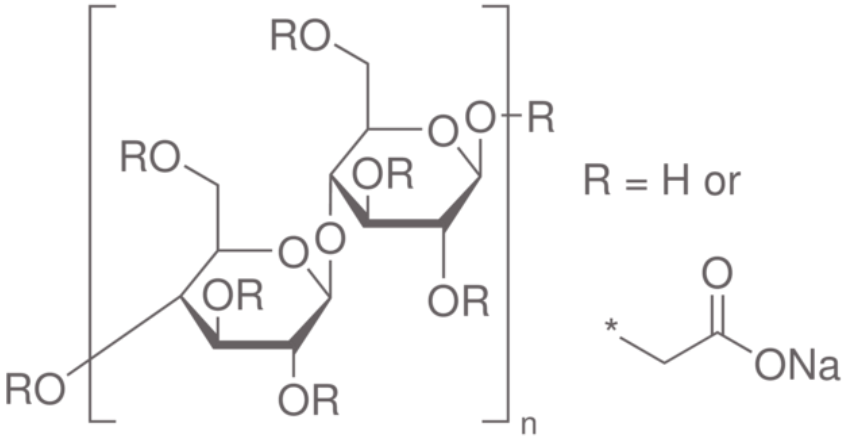
- Observe normal precautions appropriate to the circumstances and quantity of material handled.
- Eye protection and gloves are recommended.

CARBOXY METHYL CELLULOSE SODIUM

Synonym:

Cellulose gum, Sodium cellulose glycolate

Structure:



Chemical formula:

[C6H7O2(OH)x(OCH2COONa)y]n
where
n is the degree of polymerization
x = 1.50 to 2.80
y = 0.2 to 1.50
x + y = 3.0
(y = degree of substitution)

Empirical formula:

Sodium salt of poly carboxy methyl ether of cellulose

Molecular weight:

90 000 – 700 000

Description:

White to almost white, odorless, granular powder.

Solubility:

Practically insoluble in acetone, ethanol (95 %), ether and toluene. Easily dispersed in water at all temperatures forming clear, colloidal solutions.

Functional Category:

Emulsifying agent (0.25 – 1.0 %), Gel forming agent (3.0 – 6.0 %),Tablet binder (1.0-6.0 %), Coating agent, Stabilizing agent, Suspending agent, Tablet and Capsule disintegrant, viscosity increasing agent, water-absorbing agent.

LACTOSE

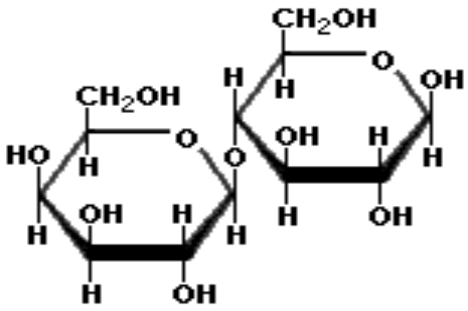
SYNONYM:

Lactopress Anhydrous.

Lactosum.

Milk sugar.

STRUCTURE: (Hand book of Pharmaceutical Excipients. Pharmaceutical Press, London. 5th edtition)



DESCRIPTION:

White to off-white crystalline particles or powder.

EMPIRICAL FORMULA:

$C_{12}H_{22}O_{11}$

MOLECULAR WEIGHT:

342.30

SOLUBILITY:

- Soluble in water,
- Sparingly soluble in ethanol (95 %) and ether.

FUNCTIONAL CATEGORY:

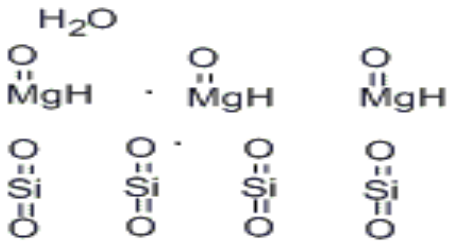
- Binding agent.
- Directly compressible excipient.
- Lyopholization aid.
- Tablet and capsule filler.

TALC

SYNONYMS:

- Powdered talc.
- Purified French chalk.
- Soapstone.

STRUCTURE: (Hand book of Pharmaceutical Excipients. Pharmaceutical Press, London. 5th edtition)



EMPIRICAL FORMULA:

$Mg_6(Si_2O_5)_4(OH)_4$

DESCRIPTION:

- **Appearance:** Very fine, unctuous, crystalline powder.
- **Colour:** White to grayish-white.
- **Odour:** Odorless, impalpable.

Solubility

Practically insoluble in dilute acids and alkalis, organic solvents, and water.

Storage Conditions

It should be stored in a tightly closed container in a cool and dry place.

Functional Category

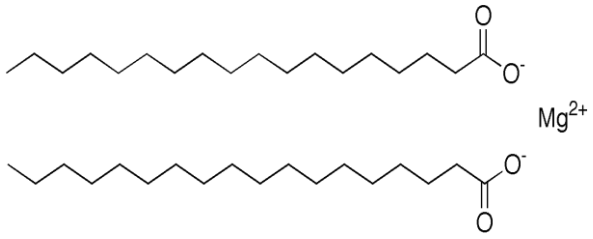
- Anti caking agent.
- Glidant.
- Lubricant.

MAGNESIUM STEARATE

SYNONYMS:

- Magnesium octadecanoate.
- Octadecanoic acid.
- Magnesium salt.

STRUCTURE: (Hand book of Pharmaceutical Excipients. Pharmaceutical Press, London. 5thedtition)



CHEMICAL NAME:

Octadecanoic acid magnesium salt

EMPIRICAL FORMULA:

$C_{36}H_{70}MgO_4$

MOLECULAR WEIGHT:

591.34

DESCRIPTION:

It is a very fine powder.

SOLUBILITY:

- Insoluble in ethanol, ether and water.
- Slightly soluble in warm benzene and warm ethanol 95%.

STABILITY AND STORAGE CONDITIONS:

It is stable and should be stored in a well closed container, in a cool, dry place.

FUNCTIONAL CATEGORY:

Tablet and capsule lubricant.

CHAPTER IX

EXPERIMENTAL PROTOCOL

CHAPTER IX

EXPERIMENTAL PROTOCOL

1. PREPARATION OF STANDARD CALIBRATION CURVE OF OLMESARTAN MEDOXOMIL

a) Preparation of phosphate buffer pH 6.8:

`A known volume of 50 ml of 0.2 M potassium dihydrogen phosphate is placed in a 200 ml volumetric flask. 22.4ml of sodium hydroxide is added and make up to the volume with distilled water. (Indian pharmacopoeia 2010)

b) Determination of λ_{max} of olmesartan medoxomil:

Standard stock solution of olmesartan medoxomil is prepared by dissolving 25mg of drug in 25ml volumetric flask using methanol as solvent. From this stock solution, working standard solution of concentration 10µg/ml is prepared by appropriate dilutions using phosphate buffer pH 6.8. Working standard solution is scanned in the entire UV range (200-400nm) to determine the λ_{max}. (Moynul Hasan et al., 2012)

c) Preparation of calibration curve of olmesartan medoxomil:

10 mg of standard olmesartan medoxomil is accurately weighed and transferred to 100 ml volumetric flask and is dissolved in methanol and diluted up to the mark with phosphate buffer pH 6.8 to produce a stock solution of 100 µg/ml. Appropriate amounts of this stock solutions are diluted with the same medium, which yield concentrations of 2-24 µg/ml. Absorbance is measured at λ_{max} using the phosphate buffer pH 6.8 as blank by U-V spectrophotometer and the calibration curve is plotted. (Moynul Hasan et al., 2012)

2. PREFORMULATION (COMPATABILITY) STUDIES

The compatibility studies are carried out by infrared spectroscopy in order to evaluate the drug and polymer interactions.

(a) Fourier Transform Infrared Spectroscopic studies (FTIR):

Fourier transform infrared (FTIR) analysis is performed to interpret the interactions of pure drug with polymers and other ingredients. Infrared spectroscopy (Model-V-5300, JASCO, Japan) is performed for pure drug, pure polymers, physical mixture of drug and polymers and drug loaded buccal tablets. All the samples are mixed with KBr and vacuum packed to obtain pellets of the materials, which are analysed. All the spectra acquired scans between 400- 4000 cm^{-1} at a resolution of $4cm^{-1}$. (Hiremath JG et al., 2009)

3. FORMULATION OF OLMESARTAN MEDOXOMIL BUCCAL ADHESIVE TABLETS

METHOD:

Direct compression method is employed to prepare buccal tablets of olmesartan medoxomil using, Carbopol 934, HPMC K15M, Xanthan Gum, Sodium carboxy methyl cellulose, Chitosan as mucoadhesive polymers.

Mucoadhesive buccal tablet each containing 20mg of olmesartan medoxomil is prepared by direct compression method. The compositions of buccal tablet formulations are given in Table. All the ingredients are passed through a 60 mesh sieve. The required quantity of drug, various polymer mixtures and fillers are mixed thoroughly. The blend is lubricated with magnesium stearate for 3-5mins and talc was added as glidant.The blend is directly compressed (8 mm diameter, round flat faced punches) using single stroke tablet punching machine. All the tablets are stored in airtight containers for further study. (Raghavendra rao N.G et al., 2012).

4. EVALUATION OF OLMESARTAN MEDOXOMIL BUCCAL ADHESIVE TABLET

(I)Pre compressional evaluation of powder blend:

(a) Bulk density (gm/ml):

Bulk density denotes the total density of the material. It includes the true volume of interparticle spaces and intraparticle pores. The packing of particles is mainly responsible for bulk. Bulk density is the ratio between a given mass of powder and its bulk volume. Apparent bulk density is determined by pouring the weighed granules into a graduated cylinder via funnel and measuring the volume. Density is calculated by using the formula, (Satyabrata Bhanja et al., 2013)

$$\text{Bulk density} = \frac{\text{Weight of the powder}}{\text{Bulk volume of powder}} = \frac{W}{V_0}$$

(b) Tapped density (gm/ml)

Aknown quantity of sample is transferred to a graduated cylinder and placed on tapped density apparatus and operated for a fixed number of taps (100).It is the ratio of weight of sample to tapped volume. (Satyabrata Bhanja et al., 2013)

$$\text{Tapped density} = \frac{\text{Weight of the powder}(W)}{\text{Tapped volume of powder}(V_f)}$$

(c) Compressibility (or) Carr's index:

Based on the apparent bulk density and the tapped density, the percentage compressibility of the bulk drug is studied by using the following formula.

$$\text{Carr's Index}(\%) = \frac{\text{Tapped Density - Bulk Density}}{\text{Tapped Density}} = \frac{\rho_t - \rho_o}{\rho_t} \times 100$$

Compressibility Index (%)	Type of Flow
5-15%	Excellent
15-25%	Good
>25%	Extremely poor

(Satyabrata Bhanja et al., 2013)

(d) Hausner's ratio

Hausner's ratio is defined as the ratio of tapped density to bulk density of the powders. The hausner's ratio is a number that is correlated to the flowability of a powder (or) granular material. It is calculated by using the formula,

$$\text{Hausner's ratio} = \frac{\rho_t}{\rho_o} \times 100$$

Where,

ρ_o= Bulk density g/ml.

ρ_t = Tapped density g/ml.

The values less than 1.25 indicate good flow (=20% Carr), whereas greater than 1.25 indicates poor flow (=33% Carr) Between 1.25 and 1.5, added glidant normally improves flow. (Satyabrata Bhanja et al., 2013)

(e) Angle of Repose (θ)

Angle of Repose is defined as the maximum angle possible between the surface of the pile of powder and horizontal plane. Angle of repose has been used as indirect methods of quantifying powder flow ability, because of their relationship with inter particle cohesion. A static heap will slide when the angle of inclination is large enough to overcome frictional forces and stop when gravitational forces balance the forces. The sides of heap will make an angle with horizontal which is called angle of repose. (Satyabrata Bhanja et al., 2013)

Angle of Repose (θ) = $\tan^{-1}(h / r)$

Where,

h = height of the heap.

r = radius of the base of the heap.

Angle of Repose (θ)	**Type of Flow**
<20°	Excellent
20° - 30°	Good
30° - 35°	Moderate
35° - 40°	Poor
>40°	Very Poor

(f) Drug Content of powder blend

A known weight of (20mg) drug equivalent of powder blend is dissolved in sufficient quantity of methanol and the volume is made up to 100 ml with phosphate buffer pH 6.8. The solution is filtered and 5ml of filtrate is diluted to 100ml with phosphate buffer pH 6.8. The absorbance of the resulting solution is measured at λmax (257 nm) using UV spectrophotometer and the drug content was determined by using the formula,

$$\text{Drug content} = \frac{\text{Sample absorbance}}{\text{Standard absorbance}} \times 100$$

(II) Post compressional evaluation of buccal adhesive tablet

(a) General appearance

The formulated tablets are evaluated for general appearance viz., colour, shape, odour, appearance etc.

(b)Tablet dimension

Thickness and diameter of five tablets randomly selected are measured using vernier calipers. The Pharmacopoeia states that the extent of deviation in a batch of tablet should not exceed the limit of ± 5% of their determined standard values. Thickness of the tablet mainly depends upon the filling, physical properties of material to be compressed and compression force. (Satyabrata Bhanja et al., 2010)

(c) Hardness test

Tablets require a certain amount of strength or hardness and resistance to friability, to withstand mechanical shocks of handling in manufacture, packaging and shipping. The hardness of the tablets is determined using Monsanto hardness tester. It is expressed in kg/cm^2. Five tablets are randomly picked from each formulation and the mean and standard deviation values are calculated and the results are shown in Table. (Satyabrata Bhanja et al., 2010)

(d) Friability test

Twenty tablets of the formulation are weighed and measured in a Roche type Friabilator (Shanghai Zhixin Instrument Co., Ltd.). The tablets were rotated at 25rpm for 4min, and the samples are then reweighed. The percentage friability was calculated using the equation: (Satyabrata Bhanja et al., 2010)

$$\text{Percentage Friability} = \frac{\text{Initial Weight} - \text{Final Weight}}{\text{Initial Weight}} \times 100$$

(e) Weight variation test

Weight variation test is done by weighing 20 tablets individually, calculating the average weight and comparing the individual weight to the average as per I.P Specification.Not more than two tablets should deviate from the percentage as given in IP and none should deviate by more than twice that percentage. (Satyabrata Bhanja et al., 2010).

The following percentage deviation in Weight Variation is Shown in the table (IP 2007)

Average Weight of a Tablet	**Percent Deviation**
80mg or less	±10%
More than 80mg but less than 250mg	±7.5%
250mg or more	±5%

(f) Estimation of drug content for tablets

A known quantity of (20mg) drug equivalent of the powdered formulation is dissolved in sufficient amount of methanol, and the volume is made up to 100ml with phosphate buffer pH 6.8 and filtered. Pipette out 5ml of the filtrate and the volume is made up to 100ml with phosphate buffer pH 6.8. A known concentration (10µg/ml) solution is prepared from the above solution and analyzed for drug content. Drug content is calculated by using the formula,

$$\text{Drug content} = \frac{\text{Sample absorbance}}{\text{Standard absorbance}} \times 100$$

(g) Determination surface pH

The surface pH of the buccal tablets is determined to investigate the chances of any side effects. As an acidic or alkaline pH may irritate the buccal mucosa, the surface pH should be close to neutral. The method used to determine surface pH of the formulation is according to reported method. In briefly, a combined glass electrode is used to measure the surface pH. The tablet is allowed to swell by keeping them in contact with distilled water (pH 6.8 ±0.01) for 2 hours and pH is noted by

bringing the electrode in contact with the surface of the formulations and allowing it to equilibrate for 1 minute. (Gaurav Kumar et al., 2011)

(h) *Ex-vivo* mucoadhesive strength

Bioadhesive strength of the buccal tablets is measured on modified physical balance used for determining the ex-vivo mucoadhesive strength of prepared buccal tablets. Fresh sheep buccal mucosa is obtained from a local slaughterhouse. The mucosal membrane is separated by removing underlying fat and loose tissues. The membrane is washed with distilled water and then with phosphate buffer pH 6.8 at 37 ± 1^{0}c. Sheep buccal mucosa was tied to the glass petri dish, which was filled with phosphate buffer so that it just touched the mucosal surface. The buccal tablet is stuck to the lower side of a thread with cyanoacrylate adhesive. The two sides of the balance are made equally by keeping a 5 g weight on the right hand pan. Next, weight of 5 gm is removed from the right hand pan, which lowered the pan along with the tablet over the mucosa. The balance is kept in this position for 5 minutes contact time. Then weight is added slowly to the right hand pan until the tablet detached from the mucosal surface. (Muthukumaran M et al., 2012)

(i)Swelling index studies

The tablets of each formulation are weighed individually (W1) and placed separately in petri-dishes containing 15ml of phosphate buffer (pH 6.8). At regular intervals (1, 2, 3, 4 and up to 12 hours) the tablets are removed from petri-dishes and excess water is removed carefully using filter paper. The swollen tablets are re-weighed (W2); the swelling index of each formulation is calculated by using this formula.

Swelling index (S.I) = W2-W1/W1

Where,

W1= Initial Weight, W2= Final Weight (Suresh Kumar P et al., 2011)

(j) *In vitro* release studies

In vitro release studies are performed in USP type II paddle apparatus for 12 hours. The tablets are placed in the dissolution medium of 900 ml phosphate buffer pH 6.8 in the dissolution apparatus. The paddle was rotated at 50 rpm maintained at 37°C. 5 ml samples are withdrawn every 15 min for the first hour and every 30 min up to 12 hours. Sink conditions are maintained after each sampling. Samples are analyzed at 257 nm using UV spectrophotometer. The studies are done in triplicate. (Gaurav Kumar et al., 2011)

(k*) In vitro* drug release kinetics studies

In controlled or sustained release formulations the three most important rate controlling mechanisms are,

- Diffusion
- Swelling and
- Erosion

The *In vitro* release profiles obtained from the floating tablets are fitted to zero order, first order, Higuchi, Hixson Crowell, Korsemeyer&Peppas model kinetics, to find out the mechanism of drug release. (Agaiah Goud B et al., 2011)

Release kinetics model	**Equation**
Zero order	$Q_t = Q_0 + K_0 t$
First order	$In\ Q_t = In\ Q_0 + K_0 t$
Hixson-Crowell	$Q_0^{1/3} – Qt^{1/3} + K t$
Higuchi	$Q = KH. t^{1/2}$
Korsmeyer – Peppas	$M_t / M_0 = a.tn$

Fitness of release profiles to linear equations is assessed by comparing the coefficients of determination (r) values.

For cylinder type of systems,

n< 0.45	:	Classical Fickian diffusion
n=0.45 to 0.89	:	Anomalous Non Fickian transport i.e. coupled drug diffusionin the hydrated matrix and polymer relaxation (Indicators of both phenomenon)
n=0.89	:	Case II relaxational release transport - Zero order release (Polymer relaxation or swelling controlled systems)
n> 0.8	:	Super Case II transport.

5. SELECTION AND EVALUATION OF BEST FORMULATION

The best formulation is selected based upon the results obtained from swelling index, *in vitro* release studies, *in vitro* kinetic studies and *in vitro* mucoadhesive strength.

(a) Infrared spectroscopic studies (IR):

Best formulation is subjected to infrared spectroscopic studies (IR) as per the procedure already discussed in compatibility studies.

(b) Differential scanning calorimetric studies (DSC):

Differential scanning calorimetry is carried out to find out any incompatibility between the drug and excipients used.

(c) Stability studies:

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, and enables

recommended storage conditions, re-test periods and shelf –lives to be established. Stability studies are carried out according to modified International conference on hormonisation (ICH) guidelines. The best formulation is kept in a stability chamber maintained at 40°C ± 5% and RH 75 % ±5% for 2 months. Samples are analyzed for the drug content, *in-vitro* drug release and other physiochemical parameters periodically. (Bhaskar Umarji et al., 2012)

CHAPTER X

RESULTS AND DISCUSSION

CHAPTER X

RESULTS AND DISCUSSION

1. PREPARATION OF STANDARD CALIBRATION CURVE OF OLMESARTAN MEDOXOMIL

(a) Preparation of phosphate buffer pH 6.8

The phosphate buffer pH 6.8 was prepared as per Indian Pharmacopoeia., 2010**.**

(b) Determination of λ_{max} of olmesartan medoxomil

The absorption maximum ($\lambda_{max)}$ of the Olmesartan medoxomil was estimated by scanning the drug solution (10µg/ml) between 200-400 nm regions on UV spectrophotometer. The obtained spectrum showed that the absorption maximum (λ_{max}) was 257nm in phosphate buffer pH 6.8 which was shown in **Figure 2a.**

(c) Preparation of calibration curve of olmesartan medoxomil

The Standard Calibration curves of Olmesartan medoxomil were prepared by using phosphate buffer pH 6.8. The absorbance was measured at λ_{max} of 257nm. The correlation coefficient was found to be 0.9995. Olmesartan medoxomil obeys the beer's law within the concentration range of (1-10µg/ml). Calibration plot of Olmesartan in phosphate buffer pH 6.8 was shown in **Table 1& Figure 2b.**

2. PREFORMULATION (COMPATABILITY) STUDIES

(a) Infrared Spectroscopic studies (IR)

Infrared spectroscopic analysis was performed to check out the compatibility between the drug (Olmesartan medoxomil) and the mucoadhesive polymers (carbopol 934P, HPMC K15M, xanthan gum, chitosan and sodium carboxy methyl cellulose) used in the formulation of buccal adhesive tablets.

IR spectrum of the drug, polymers and the physical mixtures of drug with the polymers were shown in the **Figure 3(a-l)**. Pure Olmesartan medoxomil spectra showed sharp characteristic peaks at 3291.28, 2928.38, 1832.14, 1707.78, 762.43 cm^{-1}. All the above characteristic peaks appear in the spectra of all physical mixtures.

It was found from the spectra that there was no major shifting as well as any loss of functional peaks in the spectra of drug, polymers and physical mixture of drug and polymers. This clearly indicated that there was **no interaction** between the drug and the polymers.

3. FORMULATION OF OLMESARTAN MEDOXOMIL BUCCAL ADHESIVE TABLETS

The individually weighed powder blends of each formulation were compressed in to tablets in a single punch tablet compressing machine. Each tablet contains 20mg of olmesartan medoxomil and mucoadhesive polymers such as carbopol 934P, HPMC K15M, CMC sodium, xanthan gum and chitosan in different ratios, mannitol, lactose, magnesium stearate and talc. The prepared buccal adhesive tablets were white in colour and round in shape. The ingredients for tablets of each formulation were shown in **Table 2(A, B &C)**. All the prepared tablets were found to be good without chipping, capping and sticking.

4) EVALUATION OF OLMESARTAN MEDOXOMIL BUCCAL ADHESIVE TABLET

I. Pre compression evaluation of powder blend

The powder blend of all the formulations was evaluated for the pre-compression parameters such as Bulk Density, Tapped Density, Compressibility Index, Angle of Repose, and Percentage Drug Content.

(a) Bulk Density (gm/ml)

The bulk density of the powder blend was in the range of 0.32-0.35gm/ml, which indicates, that the powder blend was not bulky. The results were shown in **Table 3 (A & B) & Figure 4.**

(b) Tapped Density (gm/ml)

The tapped density of the powder blend was in the range of 0.43-0.45 gm/ml. The results were shown **Table 3 (A & B) & Figure 5** which indicates smaller particles to occupy the voids between larger particles.

(c) Compressibility Index (I)

Compressibility index was found to be in between 19.44-23.25%, which indicates that the powder blend have the required flow property for compression. The results were shown in **Table 3 (A & B) & figure 6.**

The normal range for Compressibility index (The science of dosage form design,, M.E. Aulton Third edition)

S. No	% Compressibility Range	Flow Description
1.	5-15	Excellent (Free flowing granules
2.	12-16	Good (Free flowing powdered granules
3.	18-21	Fair (powdered granules)
4.	23-28	Poor (Very fluid powder)
5.	28-35	Poor (Fluid Cohesive powder)
6.	>40	Extremely poor (Cohesive powder)

(d) Hausner's Ratio

The Hausner's ratio of the powder blend was found to be in the range of 1.22-1.30, which indicates good flow properties of powder blend. The results were shown in **Table 3 (A & B) & figure 7**(Limit: 1.5-1.4) (The science of dosage form design, M.E. Aulton Third edition)

(e) Angle of Repose (θ)

The angle of repose for the formulated powder blend was found to be in the range of 30^0 05-32^0 47, which indicates moderate flow properties of powder blend. The results were shown in **Table 3 (A & B) & figure 8.**

(f) Drug content of powder blend

The percentage drug content for F1-F30 formulations were found to be in between 95.23-101.28% ensured the uniformity of drug content. The results were shown in **Table 3 (A& B)**. From the above results it was concluded that the angle of repose (<35^0) indicate moderate flow properties of the powder blend. This was further supported by lower compressibility index value (<25%) results in good to excellent flow properties. Powder density and hardness were often interrelated properties. In addition, powder density may influence compressibility, tablet porosity, dissolution, and other properties. All these results indicate that the powder blend of all the formulations possessed satisfactory flow properties.

II. Post compression evaluation of buccal adhesive tablets

Tablets of different formulations were subjected to evaluation tests such as general appearance, tablet dimension, hardness, friability, weight variation, drug content, determination of surface pH, Ex-vivo mucoadhesive strength, swelling index studies, in-vitro release studies, in-vitro drug release kinetic studies.

(a) General appearance

The formulated tablets were white colour, flat and round shaped without any scoring on any sides. All tablets were elegant in appearance.

(b) Tablet dimension

The thickness and diameter of all the formulations were found to be in the range of 2.4-2.5 mm & 8mm, indicates that the tablets having uniform particle size distribution and no deformity. The results were shown in **Table 4 (A&B)**

(c) Hardness

The hardness of all the formulations were found to be in the range of 6-7 Kg/cm^2 Which indicates good mechanical strength with an ability to withstand physical and chemical stress conditions while handling. The results were shown in **Table 4 (A & B)**

(d) Friability

The percentage friability of all formulations was found to be in between 0.23-0.52%. The percentage friability was less than 1% in all the formulations (I.P.Limit: less than 1%), which indicates good mechanical resistance of the tablet. The values of hardness test and percentage friability indicates good handling property of prepared tablet. The results were shown in **Table 4 (A & B)**

(e) Weight Variation

The weight variation test was performed according to the procedure given in the pharmacopoeia. All the formulated tablet (F1-F30) passes the weight variation test as the percentage weight variation was within the pharmacopoeia limits of ±7.5%

of the weight and hence all the formulations passes the weight variation within the acceptable limits as per I.P. The results were shown in **Table 4 (A & B)**

(f) Estimation of drug content for tablets

The percentage drug content of all formulations were within the range from 97.61-100.18%, showed that the drug was uniformly distributed in all the formulations, hence the percentage drug content of all the formulations complies with official specifications as per U.S.P (Limit: not less than 90% and not more than 110%) The results were shown in **Table 4 (A & B)**

(g) Determination of surface pH

Surface pH of all the formulations F1 to F30 was found to be 6.22±0.08 to 6.87±0.02, which is well within the limit of acceptable salivary pH range of 5.6 to 7.9. Hence, it was concluded that all formulations may not produce any local irritation to the mucosal surface. The results are shown in **Table 5 (A&B)**.

(C) *Ex -vivo* mucoadhesive strength

Mucoadhesive strength is the strength required to detach the tablet from the model membrane. The strength of mucoadhesion is affected by various factors such as molecular weight of polymers, contact time with mucous membrane and swelling rate of the polymer. Adhesion was reported to be effected by hydration. Hydration of the mucoadhesive polymer is essential to initiate the mucoadhesive bonding process. Once the bond is formed, reduction in the rate of swelling takes place due to water uptake from the tissue surface, only prolong the association of the tablet with the mucosa. Removal of water from the underlying mucosa layer by the hydrating polymer may increase the cohesive forces of mucus; this plays vital role in

the establishment of an effective mucoadhesive bond. Mucoadhesive force depends on the viscosity and concentration of the polymer used (Gavaskar B. et .al.,2010)**.**

The results of mucoadhesive strength were shown in the **Table 5 (A&B) & Figure 9A- 9F.** Formulation containing carbopol 934P and HPMC K15M (F1-F5), (2.5:1 ,1.5:1, 1:1, 1:1.5 & 1:2.5 ratio) showed the mucoadhesive strength of 31.8gm, 30.1gm, 27.3gm, 24.4gm & 20.9gm respectively. The mucoadhesive strength decreased in the following order

F1(2.5:1)>F2(1.5:1)>F3(1:1)>F4(1:1.5)>F5(1:2.5)

Formulation containing carbopol 934P and xanthan gum (F6-F10), (2.5:1, 1.5:1, 1:1, 1:1.5 & 1:2.5 ratio) showed the mucoadhesive strength of 31.2gm, 29.4gm, 27.9gm, 23.7gm & 20.5gm respectively. The mucoadhesive strength decreased in the following order

F6(2.5:1)>F7(1.5:1)>F8(1:1)>F9(1:1.5)>F10(1:2.5)

Formulation containing Carbapol 934 and CMC sodium (F11-F15), (2.5:1, 1.5:1, 1:1, 1:1.5 & 1:2.5 ratio) showed the mucoadhesive strength of 30.4gm, 27.3gm, 23.8gm, 20.5gm & 18.7gm respectively. The mucoadhesive strength in decreasing order is as follows

F11(2.5:1)>F12(1.5:1)>F13(1:1)>F14(1:1.5)>F15(1:2.5)

Formulation containing Carbopol 934P and chitosan (F16-F20), (2.5:1, 1.5:1, 1:1, 1:1.5 & 1:2.5 ratio) showed the mucoadhesive strength of 21.9gm, 21.9 gm, 21.7gm, 20.4gm & 19.7gm respectively. The mucoadhesive strength of decreasing order is as follows

F16(2.5:1)>F17(1.5:1)>F18(1:1)>F19(1:1.5)>F20(1:2.5)

Formulation containing HPMC K15M and CMC sodium (F21-F25), (2.5:1, 1.5:1, 1:1, 1:1.5 & 1:2.5 ratio) showed the mucoadhesive strength of 19.7gm, 18.9 gm, 18.6gm, 21.5gm & 21.4gm respectively. The mucoadhesive strength of decreasing order is as follows

F21(2.5:1)>F22(1.5:1)>F23(1:1)>F24(1:1.5)>F25(1:2.5)

Formulation containing HPMC K15M and xanthan gum (F26-F30), (2.5:1 ,1.5:1, 1:1, 1:1.5 & 1:2.5 ratio) showed the mucoadhesive strength of 21.5gm, 21.4 gm, 20.1gm, 19.6gm & 19.1gm respectively. The mucoadhesive strength of decreasing order is as follows

F26(2.5:1)>F27(1.5:1)>F28(1:1)>F29(1:1.5)>F30(1:2.5)

Buccal tablets containing carbopol 934P and HPMC K15M in the ratio of 2.5:1(F1) exhibited the highest bioadhesive strength (31.8±.35gm). The tablets containing a higher proportion of carbopol 934P showed good mucoadhesive strength. Mucoadhesive strength decreases with decrease in the carbopol concentration. The higher bioadhesive strength of carbopol may be due to the formation of secondary bioadhesion bonds with mucin and interpenetration of the polymer chains in the interfacial region, while the other polymers only undergo superficial bioadhesion. So mucoadhesive strength decreases with decreasing the carbopol 934P ratio. (Hiremath JG et al., 2009).

(h) Swelling index studies

Appropriate swelling behaviour of a buccal adhesive system is an essential property for uniform and controlled release of drug and effective mucoadhesion. Swelling index was calculated with respect to time. As time increased, the SI was

also increased, because of the weight gain by tablet is increased proportionally with rate of hydration.

Swelling study was performed on all the batches (F1-F30) for 12 hours. The results of the swelling index(SI) were given in the **Table 6 (A& B) & Figure10A-10F.** Swelling plays an important role in mucoadhesion and drug dissolution of buccal tablets.

The formulations containing carbopol 934P and HPMC K15M (F1-F5),(2.5:1, 1.5:1, 1:1, 1:1.5 & 1:2.5 ratio)showed the swelling index of 249.6%, 228.1%, 197.1%, 177%, &133% at the end of 12 hours. The rate of decrease of SI was found to be in this manner, **F1> F2 > F3 > F4> F5**

The formulations containing carbopol 934P and xanthan gum (F6-F10),(2.5:1, 1.5:1, 1:1, 1:1.5 & 1:2.5 ratio) showed the swelling index of 246.1%, 241%, 245.3%, 221.7% & 192.1 % at the end of 12 hours. The rate of decrease of SI was found to be in this manner, **F6> F7 > F8 > F9> F10**

The formulations containing carbopol 934P and CMC sodium (F11-F15), (2.5:1, 1.5:1, 1:1, 1:1.5 & 1:2.5 ratio) showed the swelling index of 238.5%, 225%, 184.1%, 128.8%, & 104.5% at the end of 12 hours. The rate of decrease of SI was found to be in this manner, **F11> F12 > F13 > F14> F15**

The formulations containing carbopol 934P and chitosan combination(F16-F20), (2.5:1, 1.5:1, 1:1, 1:1.5 & 1:2.5 ratio) showed the swelling index of 239.1%, 230.2%, 178.9%, 169.4%, &115.6% at the end of 12 hours. The rate of decrease of SI was found to be in this manner, **F16> F17 > F18 > F19> F20**

The formulations containing HPMC K15M and CMC sodium combination(F21-F25), (2.5:1, 1.5:1, 1:1, 1:1.5 & 1:2.5 ratio)showed the swelling

index of 121.6%, 119.5%, 115.1%, 121.2%, &113.4% at the end of 12 hours. The rate of decrease of SI was found to be in this manner, **F21> F22 > F23 > F24> F25**

The formulations containing HPMC K15M and Xanthan gum combination(F26-F30), (2.5:1, 1.5:1, 1:1, 1:1.5 & 1:2.5 ratio) showed the swelling index of 127.5%, 135.3%, 132.1%, 123.7%, &126.9% at the end of 12 hours. The rate of decrease of SI was found to be in this manner, **F26> F27 > F28 > F29> F30**

In this study, the higher swelling index was found for tablets of formulation 1 (F1) containing carbopol 934P and HPMC K15M in the ratio of 2.5:1. Amount of carbopol plays an important role in swelling of the matrix and leads to the drug diffusion. The hydrophilicity of carbopol 934P is greater than other polymers used, so it swells faster (Anand Padole et al., 2012). In all these formulations, it was observed that, the SI decreased on decreasing the carbopol 934P polymer concentration.

Hence, it can be concluded from the results that linear relationship exists between swelling process and bioadhesion of polymer. (Dalvadi HP et al., 2010).

(i) *In vitro* release studies

The in vitro release studies showed that the release profiles of different formulations varied according to the type and ratios of polymers. The results of in *vitro* drug release studies of all formulations shown in **Table 7A to 7F & Figure 11A-11F.**

The formulations containing carbopol 934P and HPMC K15M (F1-F5),(2.5:1, 1.5:1, 1:1, 1:1.5 & 1:2.5 ratio)showed the drug release of 249.6%, 228.1%, 197.1%, 177%, &133% at the end of 12 hours. The rate of decrease of drug release was found to be in this manner, **F1> F2 > F3 > F4> F5**

The formulations containing carbopol 934P and xanthan gum (F6-F10), (2.5:1, 1.5:1, 1:1, 1:1.5 & 1:2.5 ratio) showed the drug release of 246.1%, 241%, 245.3%, 221.7% & 192.1 % at the end of 12 hours. The rate of decrease of drug release was found to be in this manner, **F6> F7 > F8 > F9> F10**

The formulations containing carbopol 934P and CMC sodium (F11-F15), (2.5:1, 1.5:1, 1:1, 1:1.5 & 1:2.5 ratio) showed the drug release of 238.5%, 225%, 184.1%, 128.8%, & 104.5% at the end of 12 hours. The rate of decrease of drug release was found to be in this manner, **F11> F12 > F13 > F14> F15**

The formulations containing carbopol 934P and chitosan combination(F16-F20), (2.5:1, 1.5:1, 1:1, 1:1.5 & 1:2.5 ratio) showed the drug release of 239.1%, 230.2%, 178.9%, 169.4%, &115.6% at the end of 12 hours. The rate of decrease of drug release was found to be in this manner, **F16> F17 > F18 > F19> F20**

The formulations containing HPMC K15M and CMC sodium combination (F21-F25), (2.5:1, 1.5:1, 1:1, 1:1.5 & 1:2.5 ratio)showed the drug release of 121.6%, 119.5%, 115.1%, 121.2%, &113.4% at the end of 12 hours. The rate of decrease of drug release was found to be in this manner, **F21> F22 > F23 > F24> F25**

The formulations containing HPMC K15M and Xanthan gum combination(F26-F30), (2.5:1, 1.5:1, 1:1, 1:1.5 & 1:2.5 ratio) showed the drug release of 127.5%, 135.3%, 132.1%, 123.7%, &126.9% at the end of 12 hours. The rate of decrease of drug release was found to be in this manner, **F26> F27 > F28 > F29> F30**

In-vitro dissolution studies clearly indicated that the formulation 1(F1) containing carbopol 934P and HPMC K15M in the ratio of 2.5:1 showed higher drug release in a controlled manner as compared to other formulations. The release of

olmesartan medoxomil increased with increasing the amount of carbopol 934P. Carbopol 934P is more hydrophilic than HPMC K15M and other polymers; it swells rapidly, therefore decrease in carbopol content may delay the drug release. Drug release rate was increased with increasing amount of hydrophilic polymer. Another explanation includes high water uptake which leads to considerable swelling of polymer and causes drug to diffuse out from polymer matrix. Moreover the hydrophilic polymers would leach out and hence creates more pores and channels for drug to diffuse out from the device.

F1 was found to be best formulation on the basis of in vitro drug release, swelling index and mucoadhesive strength. It showed maximum drug release profile in a controlled manner at the end of 12 hours. (Hiremath JG et al., 2009).

(F) *In vitro drug* release kinetic studies

To characterize the release mechanism of olmesartan medoxomil from buccal adhesive tablets, the *in vitro* release data was subjected to various kinetic models (zero order, first order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas model). The release kinetic data for all the formulations were shown in the **Table 8 (A&B).**

The kinetic studies of all the formulations showed that zero order plots were fairly linear as indicated by their high regression values. Therefore it was ascertained that the drug release from all the formulation followed zero order kinetics (r^2=0.995 to 0.999). Formulation1 (F1) showed the closest linearity to unity ($r_=$0.999) as shown in **Figure 12A.**

All formulations exhibited a very good linearity for the Korsmeyer- peppas model. The values of n (diffusion exponent) were estimated by linear regression of log cumulative % drug release Vs log time (t) of different formulations.

The obtained values of n lie between 0.5 to 1.0 in all the formulations exhibiting a non- fickian release behaviour controlled by combination of diffusion and chain relaxation mechanism. Fitness of the data to Korsemeyer and peppas plots resulted in a linear graph with regression values close to 1 (r^2= 0.990-0.999). (Yadav Deepak R et al., 2011).

5. SELECTION AND EVALUATION OF BEST FORMULATION

The best formulation is selected based upon the results obtained from swelling index, *in vitro* release studies, *in vitro* kinetic studies and *in vitro* mucoadhesive strength.

(a) Fourier transform infrared spectroscopic studies (FTIR)

IR spectrum of the best formulation F1(carbopol and HPMC K15M in 2.5:1 ratio)was recorded. Pure olmesartan spectra showed sharp characteristic peaks at 3291.28, 2928.38, 1832.14, 1707.78, 762.43 $cm^{-1.}$ (**Figure 3 (a-l)**). All the above characteristic peaks appear in the IR spectrum of best formulation which indicates that there was no modification or interaction between drug and polymers.

(b) Differential Scanning Calorimetric (DSC) Studies

DSC thermogram of the best formulation F1 **(**carbopol and HPMC K15M in 2.5:1 ratio) was recorded. Pure olmesartan exhibits a sharp endothermic peak at 184.67^0C **(Figure 3m).** An endothermic peak corresponding to the melting point of pure drug was prominent in best formulation (F1) **(Figure 3t)**, which suggested

clearly that there was no interaction between the drug and the polymers and the drug was existed in its unchanged form.

(b) Stability Studies

Optimized formulation F1 was subjected to stability studies at 40°C±5% and RH 75%±5% RH. The results showed no significant change in the physical appearance, and in vitro release studies during storage. Thus it was found that the buccal adhesive tablets of olmesartan medoxomil were stable under these storage conditions. The results are shown in the **Table 9**. (Bhaskar Umarji et al., 2012)**.**

TABLES

TABLE 1 CALIBRATION OF OLMESARTAN MEDOXOMIL USING PHOSPHATE BUFFER pH 6.8

S.No.	CONCENTRATION (µg/ml)	ABSORBANCE AT 257nm (±SD)
1	2	0.113±0.008
2	4	0.227±0.013
3	6	0.335±0.014
4	8	0.455±0.014
5	10	0.545±0.011
6	12	0.672±0.021
7	14	0.777±0.017
8	16	0.891±0.021
9	18	0.973±0.030
10	20	1.098±0.021
11	22	1.204±0.021
12	24	1.345±0.040

n=3* r=0.9995

TABLE 2A FORMULATION OF OLMESARTAN MEDOXOMIL BUCCAL ADHESIVE TABLETS (F1-F10)

S.NO	Ingredients	Quantity (mg) for 1 tablets (Total weight 150mg)									
		F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**
1	Olmesartan medoxomil	20	20	20	20	20	20	20	20	20	20
2	Carbopol 934P	70	60	50	40	30	70	60	50	40	30
3	HPMC K15M	30	40	50	60	70	-	-	-	-	-
4	Xanthan gum	-	-	-	-	-	-	-	-	-	-
5	Sodium carboxymethyl cellulose	-	-	-	-	-	-	-	-	-	-
6	Chitosan	-	-	-	-	-	-	-	-	-	-
7	Lactose	15	15	15	15	15	15	15	15	15	15
8	Mannitol	10	10	10	10	10	10	10	10	10	10
9	Magnesium	2	2	2	2	2	2	2	2	2	2
10	Talc	3	3	3	3	3	3	3	3	3	3

TABLE 2B FORMULATION OF OLMESARTAN MEDOXOMIL BUCCAL ADHESIVE TABLETS (F11-F20)

S.NO	Ingredients	Quantity (mg) for 1 tablets (Total weight 150mg)									
		F11	**F12**	**F13**	**F14**	**F15**	**F16**	**F17**	**F18**	**F19**	**F20**
1	Olmesartan medoxomil	20	20	20	20	20	20	20	20	20	20
2	Carbopol 934P	70	60	50	40	30	70	60	50	40	30
3	HPMC K15M	-	-	-	-	-	-	-	-	-	-
4	Xanthan gum	-	-	-	-	-	-	-	-	-	-
5	Sodium carboxymethyl cellulose	30	40	50	60	70	-	-	-	-	-
6	Chitosan	-	-	-	-	-	30	40	50	60	70
7	Lactose	15	15	15	15	15	15	15	15	15	15
8	Mannitol	10	10	10	10	10	10	10	10	10	10
9	Magnesium	2	2	2	2	2	2	2	2	2	2
10	Talc	3	3	3	3	3	3	3	3	3	3

TABLE 2C FORMULATION OF OLMESARTAN MEDOXOMIL BUCCAL ADHESIVE TABLETS (F21-F30)

S.NO	Ingredients	Quantity (mg) for 1 tablets (Total weight 150mg)									
		F21	**F22**	**F23**	**F24**	**F25**	**F26**	**F27**	**F28**	**F29**	**F30**
1	Olmesartan medoxomil	20	20	20	20	20	20	20	20	20	20
2	Carbopol 934P	-	-	-	-	-	-	-	-	-	-
3	HPMC K15M	70	60	50	40	30	70	60	50	40	30
4	Xanthan gum	-	-	-	-	-	30	40	50	60	70
5	Sodium carboxymethyl cellulose	30	40	50	60	70	-	-	-	-	-
6	Chitosan	-	-	-	-	-	-	-	-	-	-
7	Lactose	15	15	15	15	15	15	15	15	15	15
8	Mannitol	10	10	10	10	10	10	10	10	10	10
9	Magnesium	2	2	2	2	2	2	2	2	2	2
10	Talc	3	3	3	3	3	3	3	3	3	3

TABLE 3A PRECOMPRESSIONAL EVALUATION OF POWER BLEND (F 1- F15)

Formulation code	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index (%)	Hausner ratio	Angle of repose (^{0})	Drug content (%)
F1	0.33±.003	0.44±.009	23±.31	1.29±.005	32.03±0.0	97.9±0.02
F2	0.32±.001	0.43±.006	23.2±.74	1.3±0.02	31.62±0.02	96.7±.01
F3	0.35±.001	0.45±.012	22.7±2.01	1.29±0.03	31.78±0.03	99.4±1.01
F4	0.35±.001	0.43±.003	19.4±0.47	1.24±0.01	32.12±0.03	99.2±.07
F5	0.33±0.03	0.43±.001	20.9±1.5	1.22±0.02	30.87±0.01	98.3±.032
F6	0.33±.005	0.44±.009	22.6±1.4	1.29±0.02	30.87±0.02	98.4±.11
F7	0.33±.007	0.43±.009	22.7±1.5	1.3±0.02	31.29±0.02	99.7±.04
F8	0.33±0.01	0.44±0	22.8±1.4	1.28±0.02	31.43±0.02	99.1±.007
F9	0.34±.008	0.43±.002	22.3±.42	1.28±0.05	31.32±0.02	98.3±.004
F10	0.33±.004	0.43±0	22±1.05	1.28±0.01	31.1±0	98.9±.02
F11	0.33±.003	0.43±0	21.78±0.74	1.27±0.01	31±0.01	97.8±.004
F12	0.34±.004	0.45±.012	22.68±0.93	1.3±.005	32.19±0.05	98.6±.012
F13	0.34±.002	0.43±.003	19.44±0.47	1.28±.005	32.47±0.01	99.2±.011
F14	0.35±0.7	0.43±.001	20.91±1.05	1.27±0.01	32.28±0.01	97.9±.003
F15	0.34±.004	0.44±.009	22.63±1.04	1.28±0.01	32.26±0.01	99.2±.002

TABLE 3B TABLE PRECOMPRESSIONAL EVALUATION OF POWER BLEND (F16- F30)

Formulation code	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index (%)	Hausner ratio	Angle of repose (^{0})	Drug content (%)
F16	0.33±0.01	0.43±.009	22.7±1.5	1.29±0.005	31.5±1.2	99.45±.001
F17	0.33±.001	0.44±0	22.81±.16	1.27±0.01	31.2±.81	99.08±.07
F18	0.32±.03	0.43±.002	22.33±.42	1.26±.005	32.29±.24	99.2±.002
F19	0.35±.002	0.43±0	22.09±1.05	1.27±0.01	31.27±.95	99.8±.001
F20	0.35±.001	0.43±0	21.78±.74	1.26±0	30.57±.27	98.9±0.02
F21	0.33±.003	0.43±.001	21.53±.92	1.24±0.01	30.8±.58	100.3±.005
F22	0.33±.007	0.43±.009	21.44±1.04	1.22±0.02	30.96±.39	98.9±0.04
F23	0.33±.011	0.44±0	22.04±0.09	1.29±0.02	30.8±.58	100.7±0.011
F24	0.33±.003	0.43±.002	21.01±0.55	1.29±0.02	30.96±.39	99.1±.006
F25	0.33±.001	0.43±0	22.33±0.42	1.3±.005	30.5±.24	101.1±.007
F26	0.33±.008	0.43±0	22.09±1.05	1.28±.017	30.8±.58	99.2±0.04
F27	0.32±.011	0.45±.012	21.78±0.74	1.28±.011	31.27±.95	99.8±0.09
F28	0.34±.004	0.43±.003	22.68±0.93	1.27±.005	31.66±.42	99.3±0.006
F29	0.33±.003	0.43±.001	19.44±0.47	1.3±.005	31.19±.39	97.9±0.002
F30	0.33±.005	0.44±.005	20.91±0.59	1.28±.005	30.9±.59	99.2±0.011

TABLE 4A POST COMPRESSION EVALUATION OF BUCCAL ADHESIVE TABLETS (F1-F15)

Formulation Code	Hardness (kg/cm^3)	Thickness (mm)	Diameter (mm)	Friability (%)	Average Weight (mg ±7.5%)*	Drug Content (%) ± S.D*
F1	6	2.4	8	0.4	151.27	99.10±0.64
F2	6	2.4	8	0.36	152.12	99.02±0.21
F3	6	2.4	8	0.23	151.4	99.63±0.12
F4	6	2.4	8	0.3	152	98.89±0.07
F5	7	2.3	8	0.4	152.25	98.17±0.11
F6	6	2.4	8	0.36	152.4	98.90±0.05
F7	6	2.4	8	0.58	152.7	98.72±0.07
F8	6	2.4	8	0.48	153.8	98.90±0.05
F9	6	2.4	8	0.36	153.1	99.82±0.64
F10	7	2.3	8	0.3	153.1	98.17±0.07
F11	6	2.4	8	0.3	153.3	99.27±0.11
F12	6	2.4	8	0.46	153.8	98.90±0.05
F13	7	2.3	8	0.36	153.5	99.27±0.06
F14	6	2.4	8	0.42	153.8	99.08±0.11
F15	6	2.4	8	0.52	153.8	99.82±0.05

n=3*

TABLE 4B POST COMPRESSION EVALUATION OF BUCCAL ADHESIVE TABLETS (F16-F30)

Formulation Code	Hardness (kg/cm^3)	Thickness (mm)	Diameter (mm)	Friability (%)	Average Weight (mg ±7.5%)*	Drug Content (%) ± S.D*
F16	6	2.4	8	0.46	152.8	98.89±0.07
F17	7	2.3	8	0.43	152.3	98.72±0.15
F18	6	2.4	8	0.42	153.9	99.63±0.08
F19	6	2.4	8	0.43	151.2	99.08±0.15
F20	6	2.4	8	0.42	152.3	97.61±0.07
F21	7	2.3	8	0.43	152.4	97.98±0.12
F22	6	2.4	8	0.33	151.9	98.35±0.14
F23	6	2.4	8	0.48	152.1	98.90±0.14
F24	6	2.4	8	0.36	152.1	98.89±0.03
F25	6	2.4	8	0.23	153.8	98.35±0.14
F26	7	2.3	8	0.39	152.4	98.72±0.16
F27	6	2.4	8	0.36	153.3	98.72±0.04
F28	6	2.4	8	0.4	151.8	99.27±0.14
F29	6	2.4	8	0.45	152.4	98.35±0.09
F30	7	2.3	8	0.3	151.9	99.08±0.13

n=3*

TABLE 5A MUCOADHESIVE STRENGTH AND SURFACE pH OF OLMESARTAN BUCCAL ADHESIVE TABLETS

Formulation code	Mucoadhesive strength(gm)	Surface pH
F1	31.8±0.35	6.67±0.12
F2	30.1±0.30	6.62±0.19
F3	27.3±0.85	6.55±0.18
F4	24.4±0.26	6.81±0.08
F5	20.9±0.36	6.59±0.11
F6	31.2±0.37	6.52±0.15
F7	29.4±0.67	6.7±0.10
F8	27.9±0.21	6.7±0.18
F9	23.7±0.37	6.54±0.24
F10	20.5±0.20	6.62±0.27
F11	30.4±0.36	6.68±0.49
F12	27.3±0.26	6.81±0.12
F13	23.8±0.26	6.77±0.24
F14	20.5±40	6.69±0.19
F15	18.7±0.30	6.73±0.07

n=3*

TABLE 5B MUCOADHESIVE STRENGTH AND SURFACE pH OF OLMESARTAN BUCCAL ADHESIVE TABLETS

Formulation code	Mucoadhesive strength(gm)	Surface pH
F16	21.9±1.25	6.61±0.14
F17	21.9±1.05	6.74±0.15
F18	21.7±1.17	6.67±0.12
F19	20.4±0.92	6.85±0.05
F20	19.7±0.47	6.57±0.18
F21	19.7±0.25	6.4±0.13
F22	19.5±0.40	6.46±0.07
F23	19.5±0.75	6.48±0.04
F24	18.9±0.30	6.65±0.11
F25	18.6±0.11	6.57±0.18
F26	21.5±1.12	6.66±0.11
F27	21.4±0.52	6.59±0.22
F28	20.0±0.25	6.82±0.04
F29	19.6±0.40	6.54±0.26
F30	19.1±0.72	6.58±0.13

n=3*

TABLE 6A SWELLING INDEX OF OLMESARTAN MEDOXOMIL BUCCAL ADHESIVE TABLETS (F1-F15)

Formulation code	Time in hours											
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
F1	36.18	44.4	64	84.3	102.6	127.1	148.3	172.5	195.4	212.5	233.3	249.6
F2	31.56	37.25	54.9	75.2	88.9	113.1	136	156.2	178.4	195	212.4	228.1
F3	38.02	47.06	58.8	73.2	81.7	104	120.5	135.4	152.3	164.6	182.8	197.1
F4	30.14	44.3	56.9	74.3	90.8	110	125.6	150	164.5	183.5	181.6	177
F5	21.1	40.5	48.3	64.1	81.7	98.1	118.9	135.3	138.6	141.8	133.9	133
F6	24	49.4	69.4	88.3	109	127.2	145.9	171.8	195.2	211.8	228.5	246.1
F7	19.7	39.6	54.5	78.5	98	118.8	139.6	161	188.9	209.1	231.2	241
F8	21.7	43.4	54.6	71.7	90.8	113.8	138.2	160.5	177.6	201.3	222.4	245.3
F9	12	31.6	45.4	61.2	71.1	94.7	115.8	141.4	159.9	182.9	199.3	221.7
F10	14.4	26.8	37.3	50.3	66.7	81.7	96.1	111.1	128.8	149.7	167.9	192.1
F11	18	37.9	56.2	73.2	93.5	115.7	133.9	154.9	174.5	197.4	216.3	238.5
F12	19	40.5	50.3	68.6	83	105.9	123.5	145.1	163.4	186.3	204	225
F13	25.2	39.1	50.3	65.6	81.5	98	111.9	128.5	138.4	153.6	164.9	184.1
F14	17.6	24.2	40.5	55.6	69.9	84.3	98	111.8	129.4	135.3	131.4	128.8
F15	18.8	29.9	43.5	59.1	68.8	83.8	93.5	100.6	118.8	124	115.6	104.5

TABLE 6B SWELLING INDEX OF OLMESARTAN MEDOXOMIL BUCCAL ADHESIVE TABLETS (F16-F30)

Formulation code	Time in hours											
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
F16	28.3	50	74.3	97.4	117.1	134.8	156.6	173	189.4	207.8	225.6	239.1
F17	29.6	48	73	94.1	115.7	130.3	150.6	166.4	184.2	199.3	215.7	230.2
F18	24.1	48.3	68.6	89.5	100.1	115.4	121.3	140.6	153.8	158.2	167.6	178.9
F19	23.7	47.3	65.7	85.4	96.5	109	119.2	134.5	146.4	149.8	156.5	169.4
F20	26.1	37.2	50.3	62	71.2	83	94.1	107.8	115.6	114.3	118.3	115.6
F21	19.6	35.9	47.1	65.4	79.7	92.8	113.7	119	128.1	118.9	122.2	121.6
F22	20.9	34	45.8	63.4	77.8	89.5	105.9	115.7	120.9	119.5	122.2	119.5
F23	20.9	37.3	49.9	64.3	75.4	85.8	95.6	108.6	120.3	118.4	115.1	115.1
F24	25.8	42.4	55.6	65.6	78.8	92.7	101.9	108.6	121.9	118.5	123.8	121.2
F25	23.8	40.3	64.7	76.5	89.7	100.9	107.5	117.4	122.7	122.7	117.4	113.4
F26	22.2	41.8	49.1	66.7	79.7	96.1	115.7	132	141.8	141.8	135.3	127.5
F27	24.2	43.8	52.9	69.8	81.7	99.3	112.5	128.8	141.8	138.6	141.8	135.3
F28	22.2	33.9	47.1	62.1	69.9	83	99.3	12.4	109.2	115.7	133.9	132.1
F29	25	33.6	44.7	56.6	71.1	80.9	90.8	107.2	117.1	113.8	117.1	123.7
F30	26.3	36.8	44.7	56.6	67.8	84.2	96.1	103.9	113.8	123	120.4	126.9

TABLE 7A INVITRO RELEASE DATA OF OLMESARTAN MEDOXOMIL BUCCAL ADHESIVE TABLETS (CARBOPOL: HPMC K15M) (F1-F5)

Time In Hours	Cumulative % Drug Release ±SD (n=3*)				
	F1(2.5:1) (%)	F2(1.5:1) (%)	F3(1:1) (%)	F4(1:1.5) (%)	F5(1:2.5) (%)
0.25	2.53±0.49	2.6±0.50	2.52±0.50	1.98±0.41	1.65±0.24
0.5	5.05±0.50	5.01±0.32	4.67±0.78	3.63±0.68	3.14±0.25
0.75	7.1±0.93	7.63±0.19	6.77±2.00	6±1.27	5.01±0.33
1	10.13±1.59	8±0.28	9.1±1.85	8.03±1.02	7.06±0.60
1.5	13.96±0.86	10.83±0.86	12.59±2.15	11.24±0.72	9.61±0.25
2	16.72±1.19	13.56±0.33	15.39±2.37	14.55±0.24	12.88±0.33
2.5	19.98±0.98	16.21±0.91	18.64±1.88	17.9±0.41	16.06±0.59
3	22.98±1.51	20.26±0.49	22.12±1.88	20.73±0.23	18.79±0.40
3.5	26.38±0.26	24.58±0.34	25.3±2.30	23.46±1.01	21.93±0.32
4	30.29±1.68	30.04±0.16	28.61±2.30	26.65±0.89	24.95±0.09
4.5	33.13±1.17	33.15±0.84	32.21±1.77	29.74±0.24	27.82±0.89
5	39.59±2.50	37.32±0.28	35.76±1.78	32.91±0.65	30.48±0.68
5.5	43.85±2.42	41.51±1.9	38.58±1.63	35.81±0.59	33.59±0.68
6	49.56±2.26	44.82±2.12	42.77±0.94	39.34±0.75	39.51±0.29
6.5	52.48±2.57	46.76±2.28	46.61±0.79	42.83±0.43	42.6±0.93
7	55.49±2.92	50.12±1.62	50.52±0.29	46.72±0.42	46.84±0.91
7.5	59.67±2.30	56.45±1.03	54.12±0.62	50.02±0.17	49.57±0.18
8	64.32±2.03	61.57±1.40	57.3±0.55	54.4±0.34	53.11±0.35
8.5	66.93±1.49	65.16±1.28	61.44±0.89	58.85±0.29	57.56±0.51
9	69.96±1.75	68.45±1.07	65.77±0.48	63.49±0.53	61.53±0.70
9.5	74.54±2.09	73.08±1.11	69.16±0.35	68.35±0.67	66.82±0.84
10	78.75±1.85	76.14±1.29	73.58±0.35	71.43±0.76	70.35±0.80
10.5	83.64±1.12	80.75±1.83	77.5±0.21	75.68±0.61	73.47±0.69
11	88.73±0.87	86.32±1.58	82.65±0.62	79.89±1.52	77.46±0.60
11.5	93.81±0.23	91.92±0.13	87.67±0.91	84.95±1.83	82.78±1.18
12	96.01±0.34	94.36±0.53	92.09±0.87	89.45±0.69	87.67±0.69

TABLE 7B INVITRO RELEASE DATA OF OLMESARTAN MEDOXOMIL BUCCAL ADHESIVE TABLETS (CARBOPOL: XANTHAN GUM) (F6-F10)

Time In Hours	Cumulative % Drug Release ±SD (n=3*)				
	F6(2.5:1) (%)	F7(1.5:1) (%)	F8(1:1) (%)	F9(1:1.5) (%)	F10(1:2.5) (%)
0.25	2.85±0.16	2.47±0.09	2.14±0.18	1.82±0.19	1.49±0.09
0.5	5.81±0.86	5.7±0.24	4.88±0.24	4.28±0.09	3.35±0.16
0.75	8.63±0.71	8.08±0.09	7.8±0.16	5.84±0.16	4.79±0.09
1	11.56±0.25	10.45±0.17	9.48±0.42	8.32±0.16	6.89±0.09
1.5	14.8±0.86	15.42±0.20	12.63±0.28	11.53±0.21	9.28±0.24
2	18.49±0.17	18.65±0.33	15.93±0.33	14.82±0.16	12.63±0.31
2.5	21.59±0.26	21.7±0.43	19.75±0.19	17.14±0.25	14.66±0.26
3	25.15±0.51	25.04±0.18	22.91±0.33	20.51±0.09	17.56±0.32
3.5	28.34±0.60	28.34±0.16	26.58±0.41	23.19±0.24	19.51±0.41
4	31.61±0.59	31.72±0.09	29.29±0.25	26.16±0.24	22.35±0.16
4.5	35.11±1.07	35.87±0.16	33.17±0.33	29.36±0.09	25.53±0.25
5	38.53±2.01	39.4±0.24	36.73±0.58	32.96±0.24	29.27±0.10
5.5	42.94±2.12	43.81±0.16	40.26±0.32	37.07±0.24	32.33±0.19
6	47.54±1.24	47.6±0.34	45.12±0.41	40.76±0.09	36.6±0.34
6.5	50.53±1.94	50.75±0.19	47.93±0.31	44.15±0.16	39.42±0.24
7	54.45±0.54	54.14±0.25	52.22±0.34	46.95±0.24	43.45±0.41
7.5	57.53±0.82	57.87±0.19	55.84±0.50	49.72±0.33	46.68±0.33
8	61.82±0.60	60.39±0.33	58.76±0.59	53.2±0.24	49.34±0.34
8.5	65.43±0.32	65.22±0.66	61.69±0.49	56.71±0.19	52.93±0.34
9	68.94±0.66	69.77±0.15	65.13±0.60	60.01±0.25	55.62±0.40
9.5	73.4±0.73	72.05±0.34	69.24±0.30	63.99±0.17	59.13±0.25
10	77.61±0.84	75.49±0.18	72.83±0.24	67.71±0.19	63.6±0.26
10.5	81.19±0.46	79.05±0.41	76.38±0.41	72.44±0.08	67.04±0.42
11	84.78±0.66	83.34±0.19	79.84±0.40	76.31±0.17	71.88±0.28
11.5	90.79±1.23	87.65±0.32	84.08±0.34	80.43±0.23	76.13±0.24
12	93.56±0.19	91.44±0.34	88.45±0.32	84.51±0.10	80.68±0.17

TABLE 7C INVITRO RELEASE DATA OF OLMESARTAN MEDOXOMIL BUCCAL ADHESIVE TABLETS (CARBOPOL: CMC SODIUM) (F11-F15)

Time In Hours	Cumulative % Drug Release ±SD (n=3*)				
	F11(2.5:1) (%)	F12(1.5:1) (%)	F13(1:1) (%)	F14(1:1.5) (%)	F15(1:2.5) (%)
0.25	2.91±0.09	2.47±0.09	2.09±0.09	1.98±0.09	1.76±0.24
0.5	5.27±0.24	4.88±0.09	4.55±0.24	4.63±0.49	4.12±0.57
0.75	7.92±0.19	7.48±0.16	6.88±0.33	6.44±0.24	5.94±0.41
1	10.55±0.27	9.81±0.16	8.77±0.33	8.5±0.43	7.78±0.34
1.5	14.35±0.41	13.47±0.24	12.37±0.24	11.43±0.35	10.93±0.24
2	17.71±0.24	16.76±0.24	15.71±0.52	15.53±0.54	14.27±0.41
2.5	21.57±0.32	19.75±0.24	19.18±0.16	18.46±0.58	16.97±0.84
3	24.58±0.32	23.52±0.24	22.62±0.34	20.61±0.75	20.28±0.41
3.5	28.38±0.24	26.6±0.24	25.31±0.16	23.42±0.51	22.8±0.32
4	31.64±0.19	30.45±0.24	28.45±0.24	26.4±0.34	25.38±0.49
4.5	35.8±0.24	34.5±0.33	31.93±0.41	30.2±0.43	28.25±0.25
5	40.36±0.24	38.84±0.25	35.88±0.24	33.2±0.51	30.8±0.10
5.5	44.84±0.19	44.12±0.40	40.17±0.41	36.98±0.34	35.06±0.25
6	49.23±0.25	48.02±0.33	44.7±0.5	40.52±0.34	38.64±0.33
6.5	52.99±0.29	51.5±0.41	49.2±0.33	44.61±0.43	42.29±0.33
7	56.34±0.42	55.05±0.24	52.46±0.24	48.18±0.66	46.06±0.49
7.5	60.84±0.41	58.19±0.25	54.93±0.18	51.66±0.64	49.42±0.35
8	63.73±0.50	61.94±0.25	57.84±0.18	55.54±0.27	52.75±0.24
8.5	68.39±0.67	66.03±0.41	62.96±0.32	58.67±0.51	55.81±0.51
9	71.81±0.34	70.43±0.34	67±0.34	62.42±0.59	60.31±0.32
9.5	75.57±0.35	73.96±0.50	70.91±0.35	66.63±0.40	64.35±0.25
10	79.74±0.26	77.08±0.25	74.51±0.32	71.14±0.61	68.07±0.26
10.5	83.6±0.37	81.42±0.24	79.32±0.50	74.9±0.28	72.14±0.34
11	87.26±0.43	85.07±0.33	82.74±0.42	79.06±0.44	76.02±0.42
11.5	91.27±0.34	88.85±0.24	86.62±0.43	83.57±0.44	79.91±0.48
12	94.14±0.43	92.26±0.24	89.36±0.23	86.96±0.45	83.77±0.77

TABLE 7D INVITRO RELEASE DATA OF OLMESARTAN MEDOXOMIL BUCCAL ADHESIVE TABLETS (CARBOPOL: CHITOSAN) (F16-F20)

Time In Hours	Cumulative % Drug Release ±SD (n=3*)				
	F16(2.5:1) (%)	F17(1.5:1) (%)	F18(1:1) (%)	F19(1:1.5) (%)	F20(1:2.5) (%)
0.25	2.8±0.09	2.47±0.24	1.76±0.18	1.71±0.33	1.49±0.33
0.5	5.1±0.24	4.72±0.19	4.06±0.24	3.95±0.41	3.08±0.24
0.75	7.81±0.33	7.1±0.19	6.54±0.24	6.27±0.73	5.56±0.09
1	10.14±0.33	9.64±0.16	9.04±0.09	8.87±0.25	7.44±0.41
1.5	14.84±0.24	13.4±0.26	12.72±0.22	11.85±0.32	10.46±0.22
2	16.99±0.49	16.43±0.49	15.29±0.27	14.88±0.39	13.44±0.24
2.5	20.64±0.24	19.52±0.16	18.85±0.32	17.96±0.19	16.68±0.32
3	24.74±0.49	22.69±0.24	21.41±0.28	19.99±0.25	18.25±0.32
3.5	27.77±0.25	26.09±0.34	23.88±0.19	22.87±0.34	21.68±0.41
4	30.92±0.33	29.13±0.49	27.61±0.25	25.89±0.33	24.31±0.50
4.5	35.18±0.28	33.49±0.33	31.26±0.40	28.93±0.25	27.06±0.58
5	39.2±0.57	37.01±0.93	34.37±0.41	32.8±0.49	30.32±0.34
5.5	44.16±0.40	42.06±0.43	38.28±0.33	36.03±0.33	34.03±0.41
6	48.01±0.33	45.41±0.32	42.25±0.41	39.72±0.25	37.17±0.26
6.5	51.21±0.34	48.71±0.41	45.81±0.50	43.15±0.32	40.42±0.32
7	54.49±0.34	52.46±0.49	49.06±0.59	46.44±0.66	43.91±0.15
7.5	57.73±0.57	55.8±0.41	52.92±0.32	50.57±0.42	47.54±0.56
8	61.48±0.58	59.32±0.40	56.26±0.41	53.9±0.34	51.23±0.49
8.5	65.35±0.63	62.59±0.19	59.29±0.40	57.24±0.41	54.45±0.58
9	68.7±0.50	66.14±0.28	62.5±0.74	60.88±0.34	57.75±0.33
9.5	72.83±0.51	69.76±0.31	66.05±0.53	63.71±0.39	61.11±0.42
10	77.04±0.34	73.68±0.17	69.46±0.25	67±0.48	64.82±0.24
10.5	81.05±0.35	77.62±0.23	72.94±0.25	70.57±0.31	68.66±0.42
11	84.86±0.26	81.52±0.40	76.32±0.96	74.16±0.40	72.45±0.25
11.5	88.53±0.42	85.39±0.49	80.6±0.75	78.1±0.33	75.84±0.51
12	92.05±0.48	89.27±0.41	84.35±0.59	80.91±0.59	78.64±0.34

TABLE 7E INVITRO RELEASE DATA OF OLMESARTAN MEDOXOMIL BUCCAL ADHESIVE TABLETS (CARBOPOL: CHITOSAN) (F21-F25)

Time In Hours	Cumulative % Drug Release ±SD (n=3*)				
	F21(2.5:1) (%)	F22(1.5:1) (%)	F23(1:1) (%)	F24(1:1.5) (%)	F25(1:2.5) (%)
0.25	2.8±0.41	2.75±0.19	2.52±0.16	1.98±0.33	1.65±0.18
0.5	5.65±0.28	4.88±0.24	4.67±0.33	3.63±0.19	3.14±0.33
0.75	7.81±0.16	7.48±0.16	6.77±0.24	6±0.33	5.01±0.16
1	10.64±0.33	9.86±0.24	9.1±0.19	8.03±0.41	7.06±0.33
1.5	13.53±0.24	12.5±0.17	12.59±0.24	11.24±0.22	9.61±0.24
2	17.16±0.33	16.11±0.41	15.39±0.24	14.55±0.24	12.88±0.09
2.5	21.18±0.49	19.36±0.28	18.64±0.08	17.9±0.25	16.06±0.25
3	24.63±0.18	23.23±0.32	22.12±0.24	20.73±0.16	18.79±0.26
3.5	28.59±0.24	27.13±0.16	25.3±0.32	23.46±0.17	21.93±0.16
4	31.64±0.41	30.82±0.41	28.61±0.25	26.65±0.25	24.95±0.24
4.5	35.31±0.24	33.78±0.24	32.21±0.24	29.74±0.25	27.82±0.24
5	39.37±0.25	37.84±0.24	35.76±0.49	32.91±0.17	30.48±0.24
5.5	43.79±0.32	40.72±0.24	38.58±0.17	35.81±0.23	33.59±0.25
6	47.63±0.32	44.76±0.49	42.77±0.25	39.34±0.29	36.51±0.25
6.5	51.93±0.41	48.55±0.34	46.61±0.25	42.83±0.15	39.6±0.17
7	55.37±0.32	52.52±0.41	50.52±0.41	46.72±0.50	42.81±0.25
7.5	58.23±0.24	56.03±0.17	54.12±0.44	50.02±0.34	46.15±0.25
8	62.15±0.24	59.88±0.41	57.3±0.50	53.4±0.34	49.57±0.25
8.5	65.76±0.49	63.58±0.26	60.44±0.60	56.85±0.23	53.11±0.25
9	69.71±0.41	67.09±0.23	63.77±0.54	60.49±0.33	56.56±0.16
9.5	73.84±0.58	70.88±0.25	67.16±0.51	64.3±0.17	59.53±0.26
10	77.4±0.33	74.69±0.25	70.58±0.69	67.43±0.16	62.85±0.25
10.5	81.36±0.25	78.42±0.44	74.5±0.78	70.68±0.25	66.35±0.60
11	85.45±0.34	82.49±0.42	78.65±0.48	73.89±0.16	70.47±0.31
11.5	89.34±0.34	86.74±0.26	82.67±0.52	76.95±0.24	73.78±0.18
12	92.42±0.50	89.87±0.34	87.09±0.43	80.19±0.33	76.68±0.08

TABLE 7F INVITRO RELEASE DATA OF OLMESARTAN MEDOXOMIL BUCCAL ADHESIVE TABLETS (HPMC K15M: XANTHAN GUM) (F26-F30)

Time In Hours	Cumulative % Drug Release ±SD (n=3*)				
	F26(2.5:1) (%)	F27(1.5:1) (%)	F28(1:1) (%)	F29(1:1.5) (%)	F30(1:2.5) (%)
0.25	2.74±0.24	2.52±0.43	2.36±0.32	2.03±0.16	1.97±0.09
0.5	5.1±0.18	4.88±0.24	4.61±0.19	4.01±0.16	3.52±0.16
0.75	7.32±0.33	7.26±0.24	6.82±0.16	6.54±0.24	5.45±0.09
1	9.49±0.33	9.59±0.25	8.71±0.24	8.65±0.16	7.5±0.16
1.5	12.97±0.57	12.38±0.24	12.04±0.24	11.6±0.19	10.31±0.14
2	16.11±0.59	15.61±0.41	15±0.28	14.72±0.25	13.38±0.24
2.5	19.53±0.34	18.7±0.16	19.39±2.5	17.64±0.41	16.14±0.09
3	23.24±0.34	21.43±0.17	20.37±0.10	20.47±0.50	19.28±0.41
3.5	26.53±0.58	24.87±0.66	22.73±0.37	23.25±0.69	21.79±0.28
4	30.55±0.50	27.63±0.58	25.64±0.25	25.46±0.67	24.47±0.25
4.5	34.38±0.51	31.93±0.25	28.45±0.26	28±0.73	27.23±0.25
5	38.11±0.35	34.99±0.24	31.22±0.35	30.61±1.01	29.89±0.33
5.5	42.2±0.58	38.73±0.29	34.5±0.43	33.06±0.88	32.78±0.41
6	45.43±0.72	42.22±0.31	37.42±0.59	35.76±0.92	35.3±0.60
6.5	49.06±0.44	45.01±0.24	40.3±0.52	38.62±0.56	38.01±0.99
7	52.44±0.44	48.91±0.99	43.41±0.76	41.78±0.44	40.51±1.08
7.5	56.42±0.28	51.69±0.81	46.53±1.10	45.22±0.28	43.29±0.77
8	60.33±0.37	54.91±0.68	50.06±1.37	49.01±0.36	46.47±0.62
8.5	63.93±0.40	58.04±0.51	53.38±1.52	52.49±0.56	49.77±0.55
9	66.67±0.42	61.68±0.30	56.83±1.28	50.15±0.79	53.15±0.71
9.5	69.8±0.34	65.06±0.26	60.25±0.88	59.043±0.33	56.16±0.61
10	72.58±0.23	68.41±0.29	63.73±0.64	62.25±0.35	59.19±0.53
10.5	75.85±0.39	71.61±0.25	67.51±0.47	65.85±0.42	62.23±0.62
11	79.42±0.20	75.1±0.25	71.3±0.31	69.31±0.42	65.61±0.54
11.5	82.51±0.29	78.66±0.25	75±0.15	72.51±0.44	69.07±0.66
12	85.34±0.51	82.07±0.24	78.45±0.26	75.3±0.25	72.60±0.46

TABLE 8A KINETIC STUDIES FOR OLMESARTAN MEDOXOMIL BUCCAL ADHESIVE TABLETS

FORMULATION CODE	ZERO ORDER		FIRST ORDER		HIGUCHI MODEL		HIXON – CROWELL MODEL		KORS-MEYER & PEPPAS MODEL	
	R^2	K_0 h^{-1}	R^2	K_1 h^{-1}	R^2	K_H $h^{1/2}$	R^2	K_{HC} $h^{1/3}$	R^2	n
F1	0.999	7.387	0.836	-0.09	0.954	32.37	0.929	-0.222	0.996	0.928
F2	0.998	7.916	0.849	-0.082	0.943	31.79	0.941	-0.198	0.99	0.938
F3	0.997	7.378	0.87	-0.072	0.946	30.09	0.938	-0.19	0.997	0.919
F4	0.998	7.539	0.884	-0.066	0.937	29.35	0.939	-0.179	0.997	0.968
F5	0.995	7.133	0.898	-0.063	0.937	29.1	0.947	-0.173	0.997	1.018
F6	0.998	7.539	0.874	-0.079	0.958	30.77	0.945	-0.202	0.996	0.868
F7	0.999	7.387	0.909	-0.073	0.967	30.25	0.963	-0.192	0.997	0.887
F8	0.999	7.539	0.924	-0.066	0.962	29.38	0.967	-0.178	0.997	0.917
F9	0.998	6.817	0.923	-0.058	0.95	27.85	0.961	-0.162	0.997	0.95
F10	0.995	6.506	0.925	-0.051	0.938	26.54	0.959	-0.148	0.997	1
F11	0.999	7.795	0.889	-0.084	0.963	31.92	0.955	-0.213	0.998	0.897
F12	0.999	7.646	0.906	-0.078	0.962	31.33	0.961	-0.202	0.998	0.923
F13	0.999	7.418	0.913	-0.07	0.955	30.35	0.96	-0.189	0.998	0.945
F14	0.997	7.072	0.91	-0.063	0.946	28.84	0.955	-0.173	0.996	0.938
F15	0.997	6.813	0.923	-0.057	0.944	27.79	0.96	-0.161	0.997	0.957

TABLE 8B KINETIC STUDIES FOR OLMESARTAN MEDOXOMIL BUCCAL ADHESIVE TABLETS

FORMULATION CODE	ZERO ORDER		FIRST ORDER		HIGUCHI MODEL		HIXON – CROWELL MODEL		KORS-MEYER & PEPPAS MODEL	
	R^2	K_0h^{-1}	R^2	K_1h^{-1}	R^2	$K_Hh^{1/2}$	R^2	$K_{HC}h^{1/3}$	R^2	n
F16	0.999	7.53	0.903	-0.076	0.963	30.83	0.959	-0.198	0.998	0.894
F17	0.999	7.283	0.919	-0.068	0.961	29.82	0.965	-0.184	0.998	0.913
F18	0.999	6.887	0.941	-0.059	0.961	28.2	0.973	-0.164	0.996	0.949
F19	0.998	6.661	0.948	-0.054	0.956	27.24	0.975	-0.155	0.996	0.948
F20	0.998	6.502	0.946	-0.051	0.949	26.58	0.972	-0.148	0.997	0.991
F21	0.999	7.587	0.901	-0.078	0.963	31.06	0.959	-0.201	0.998	0.89
F22	0.999	7.364	0.913	-0.07	0.96	30.13	0.962	-0.188	0.998	0.901
F23	0.999	7.041	0.925	-0.062	0.959	28.8	0.966	-0.172	0.998	0.908
F24	0.999	6.638	0.953	-0.054	0.959	27.18	0.978	-0.153	0.998	0.948
F25	0.999	6.313	0.953	-0.048	0.954	25.84	0.976	-0.141	0.999	0.982
F26	0.998	7.114	0.955	-0.063	0.97	29.21	0.983	-0.174	0.999	0.893
F27	0.999	6.683	0.951	-0.055	0.963	27.35	0.979	-0.157	0.998	0.883
F28	0.997	6.254	0.942	-0.049	0.951	25.45	0.972	-0.148	0.996	0.875
F29	0.997	6.083	0.952	-0.046	0.953	24.82	0.971	-0.134	0.996	0.896
F30	0.998	5.838	0.962	-0.042	0.958	23.88	0.981	-0.126	0.999	0.921

TABLE 9. STABILITY STUDY (40^0C/75% RH) OF BEST FORMULATION (F1)

CARBOPOL 934P:HPMC K15M (2.5:1)

S. No	Parameters	Intervals of testing		
		At 0 days	**At 30 days**	**At 60 days**
1	Physical appearance	White colour, flat shaped	White colour, flat shaped	White colour, flat shaped
2	Hardness (kg/cm2)	7.0	7.0	7.0
3	Thickness (mm)	2.4	2.4	2.4
4	Drug content (%)	99.3	98.8	98.69
5	Mucoadhesive strength(g)	31.8	31.5	31.5
6	Surface pH	6.67	6.69	6.76

FIGURES

FIGURE 2a: CALIBRATION OF OLMESARTAN MEDOXOMIL

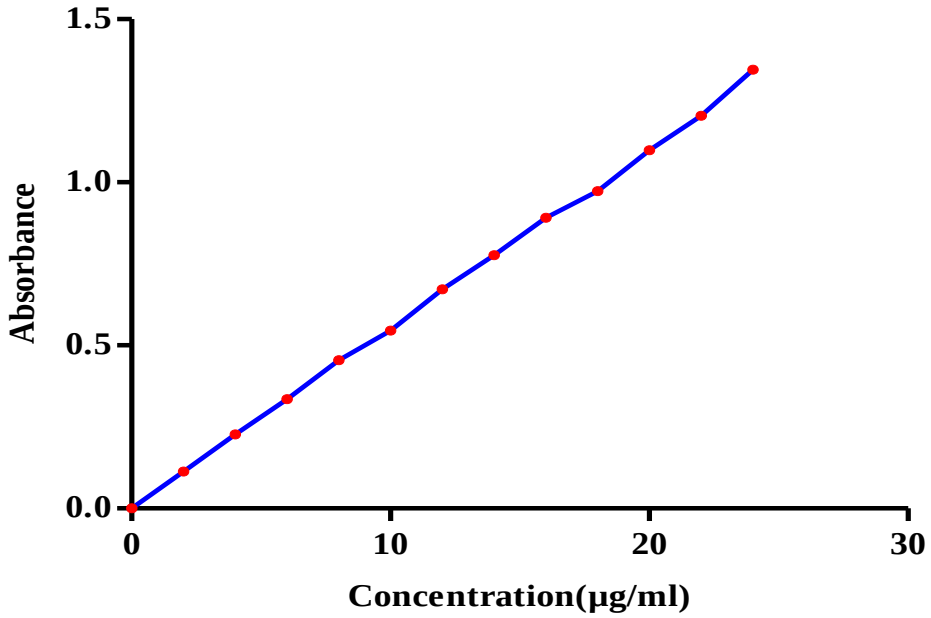


FIGURE 2b: DETERMINATION OF λ_{MAX} OF OLMESARTAN MEDOXOMIL

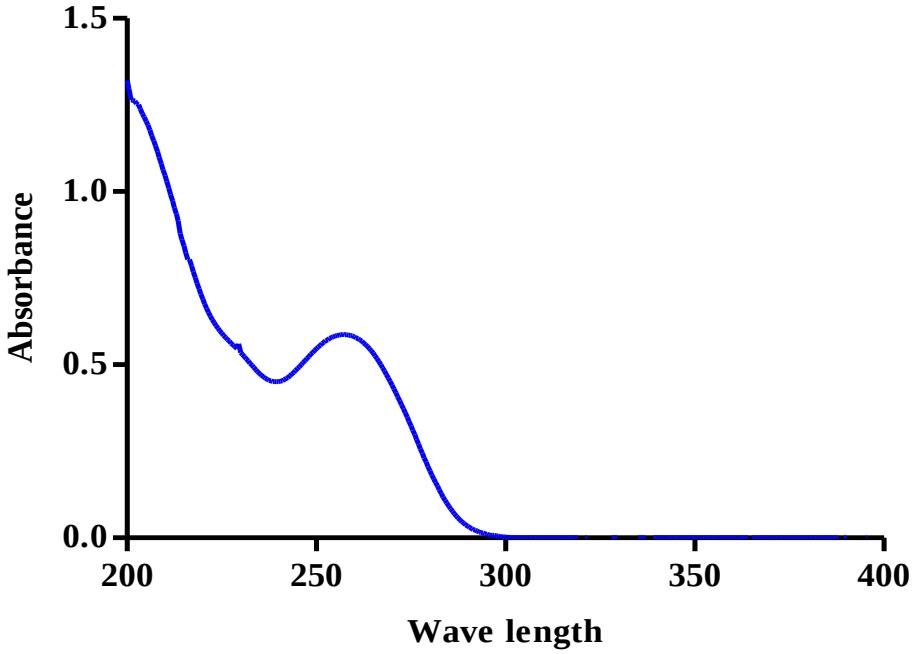


FIGURE 3a: FTIR SPECTRUM OF OLMESARTAN

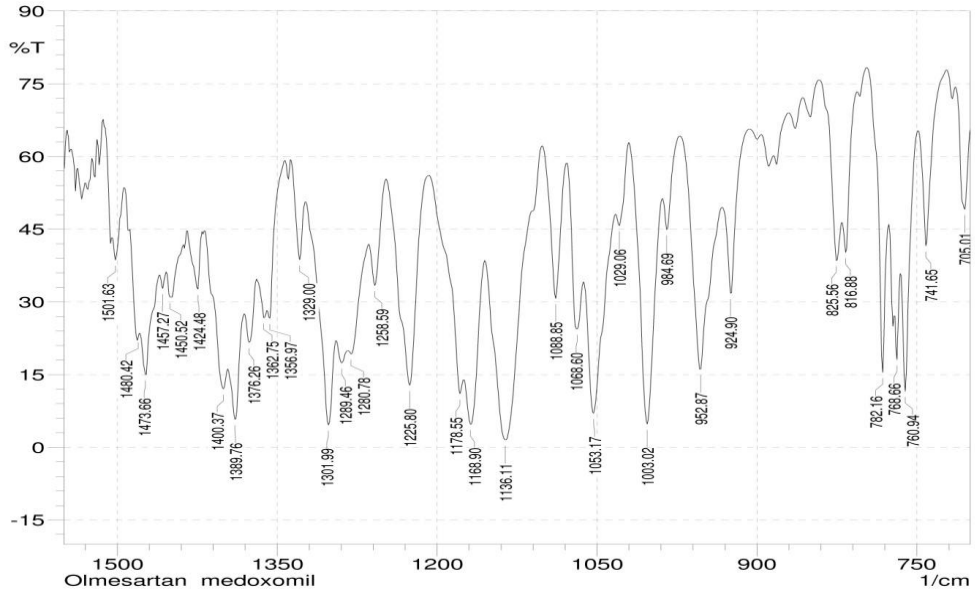


FIGURE 3b: FTIR SPECTRUM OF CARBOPOL 934P

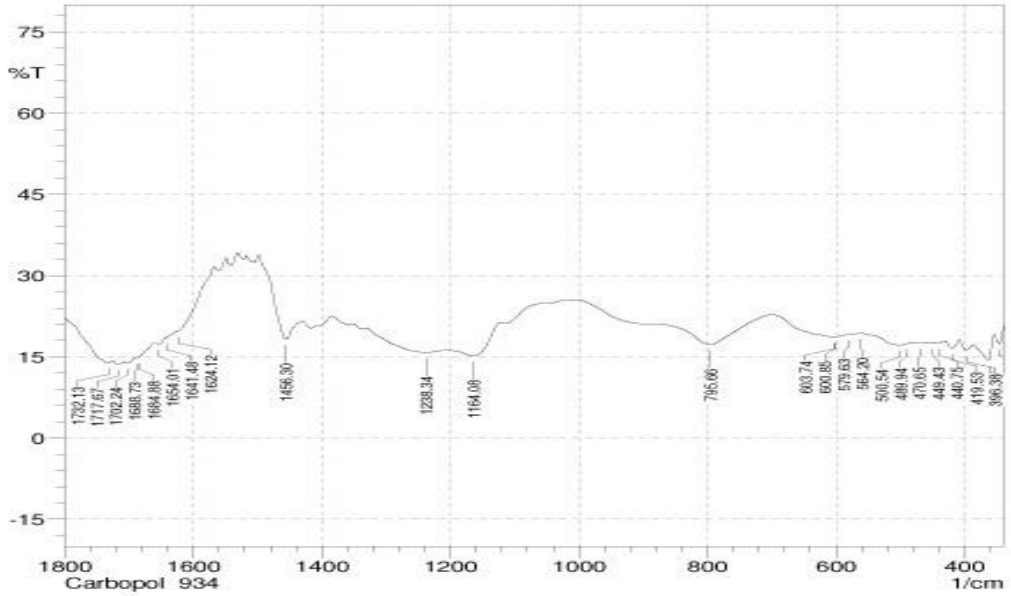


FIGURE 3c: FTIR SPECTRUM OF HPMC K15M

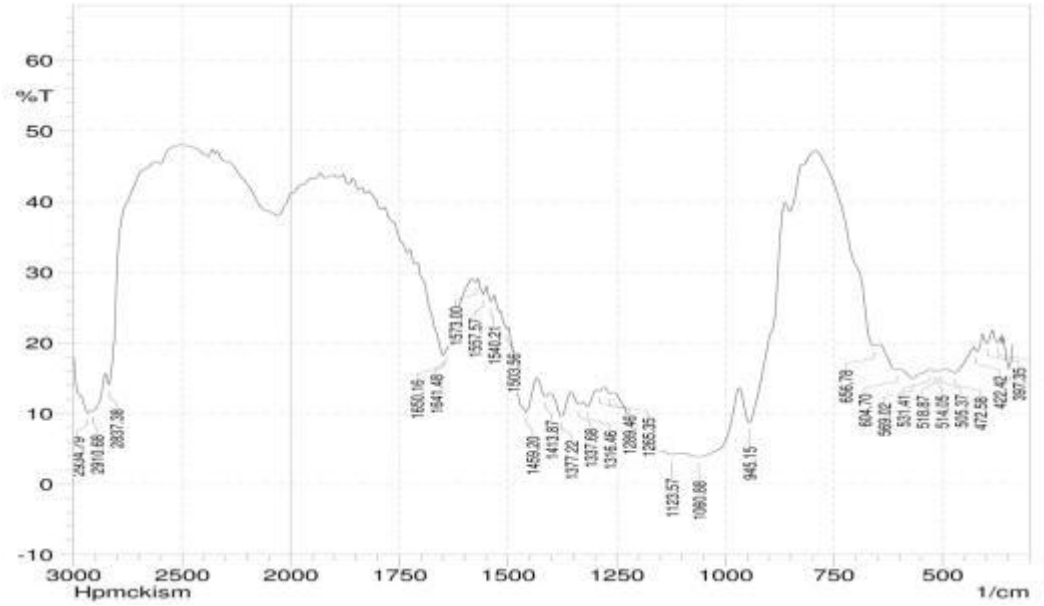


FIGURE 3d: FTIR SPECTRUM OF CHITOSAN

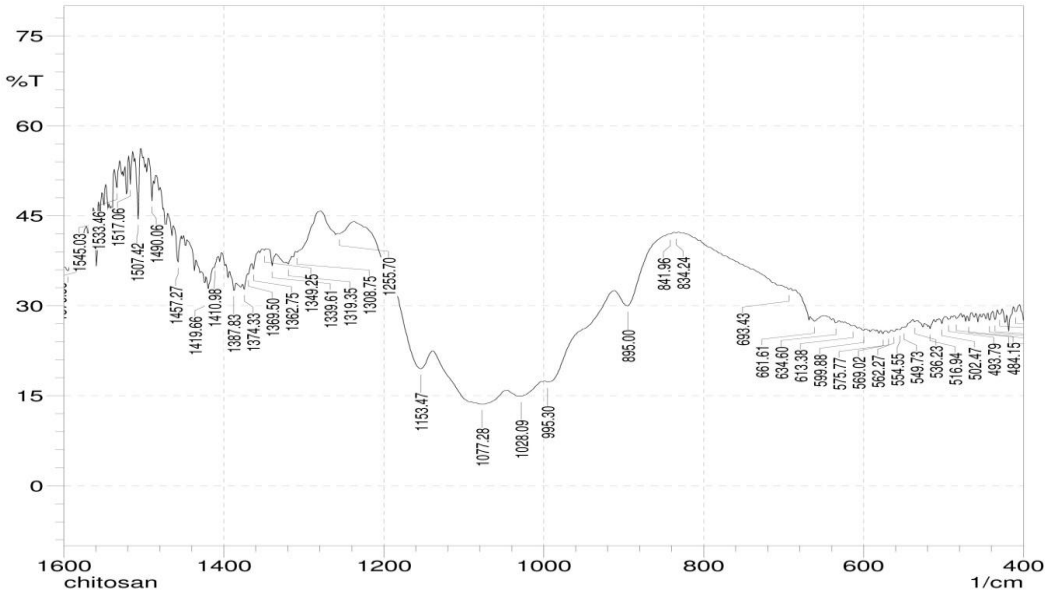


FIGURE 3e: FTIR SPECTRUM OF CMC SODIUM

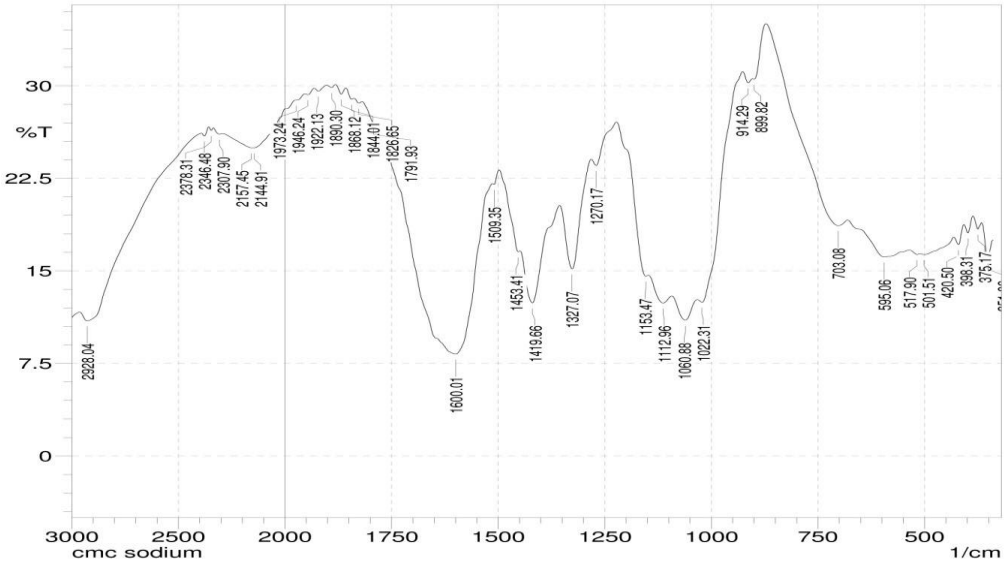


FIGURE 3f:FTIR SPECTRUM OF XANTHAN GUM

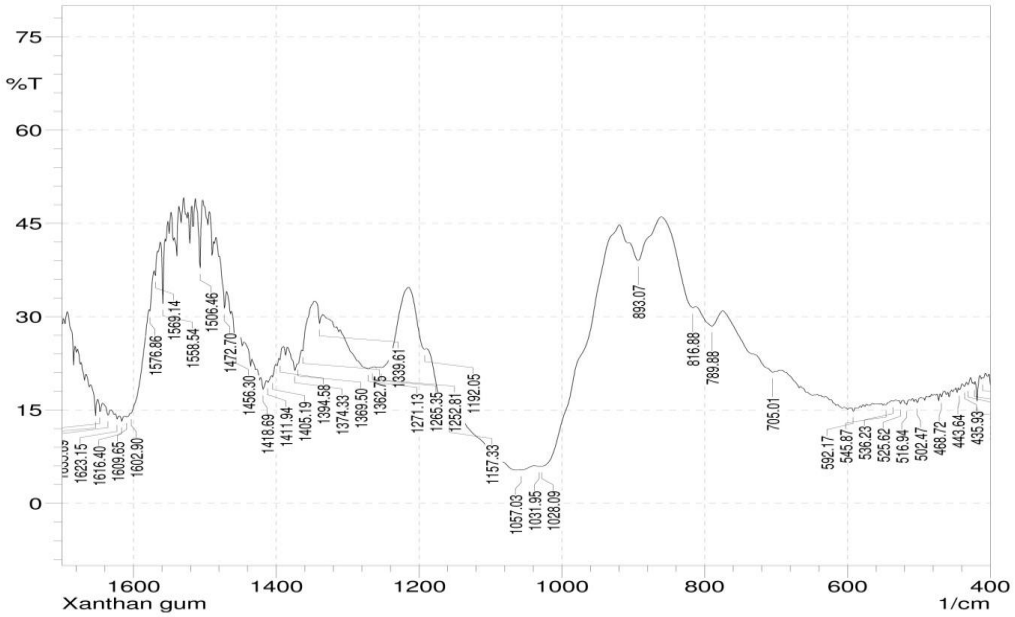


FIGURE 3g: FTIR SPECTRUM OF OLMESARTAN, CARBOPOL 934P AND CMC SODIUM

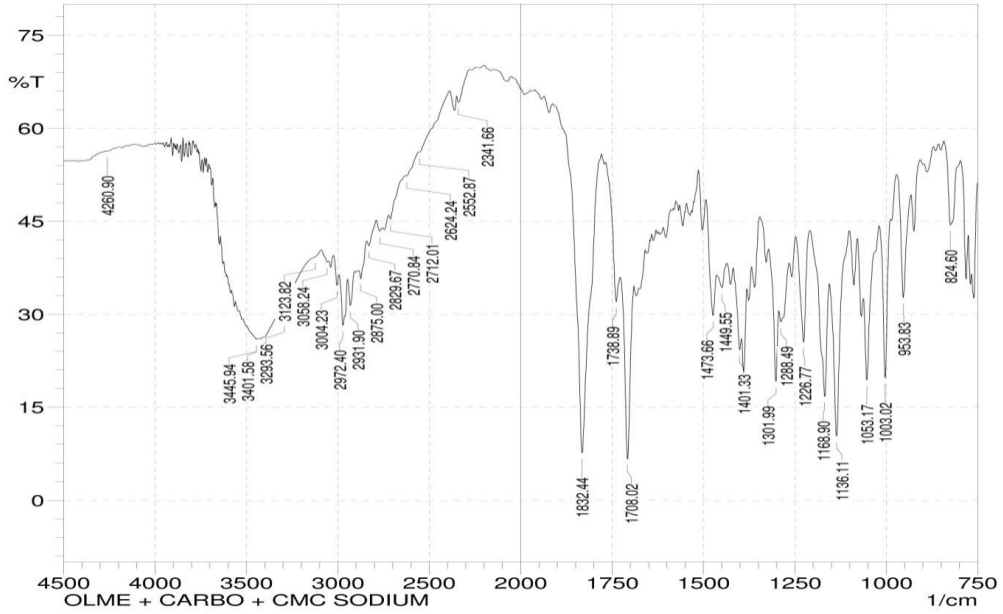


FIGURE 3h: FTIR SPECTRUM OF OLMESARTAN, CARBOPOL 934P AND CHITOSAN

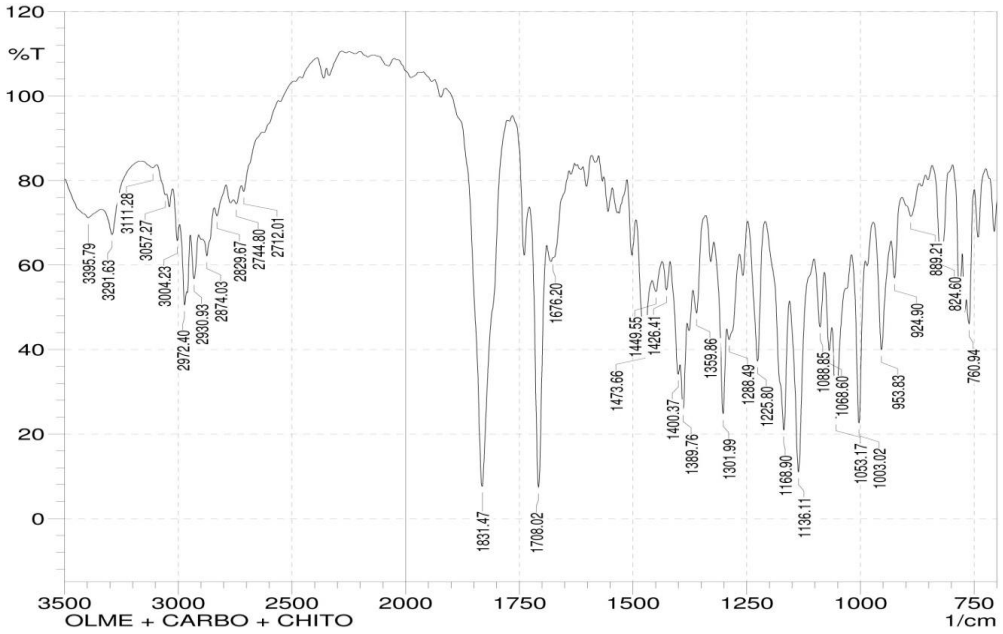


FIGURE 3i: FTIR SPECTRUM OF OLMESARTAN, CARBOPOL 934P AND HPMC K15M

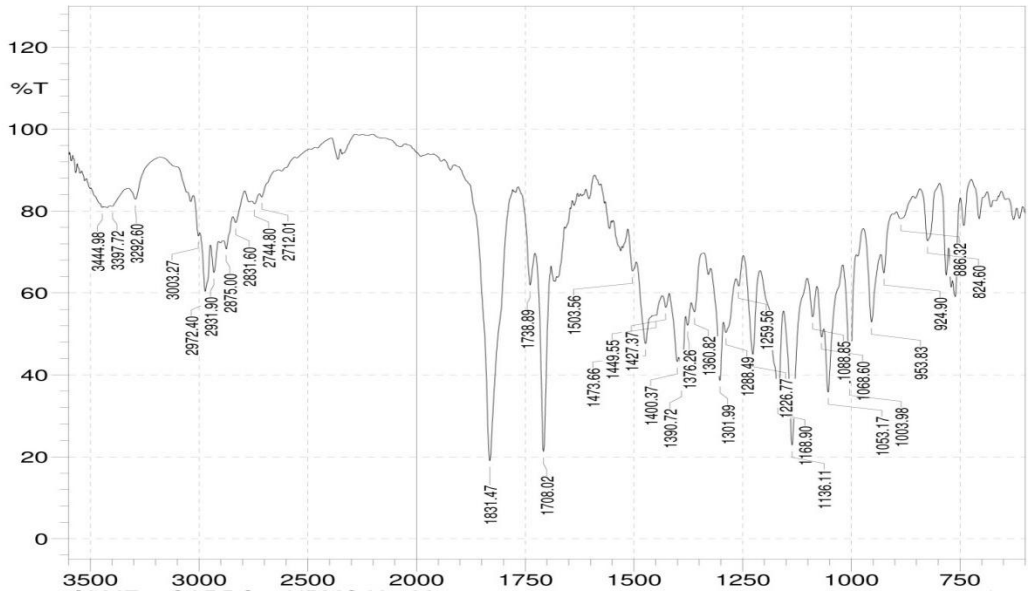


FIGURE 3j: FTIR SPECTRUM OF OLMESARTAN, CMC SODIUM AND HPMC K15M

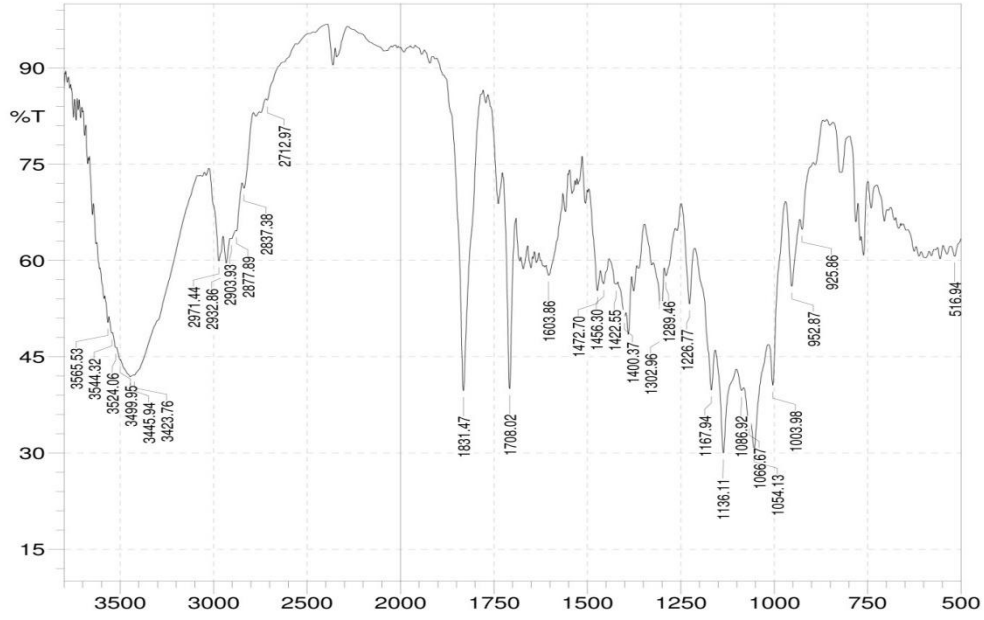


FIGURE 3k:FTIR SPECTRUM OF OLMESARTAN, CARBOPOL 934P AND XANTHAN GUM

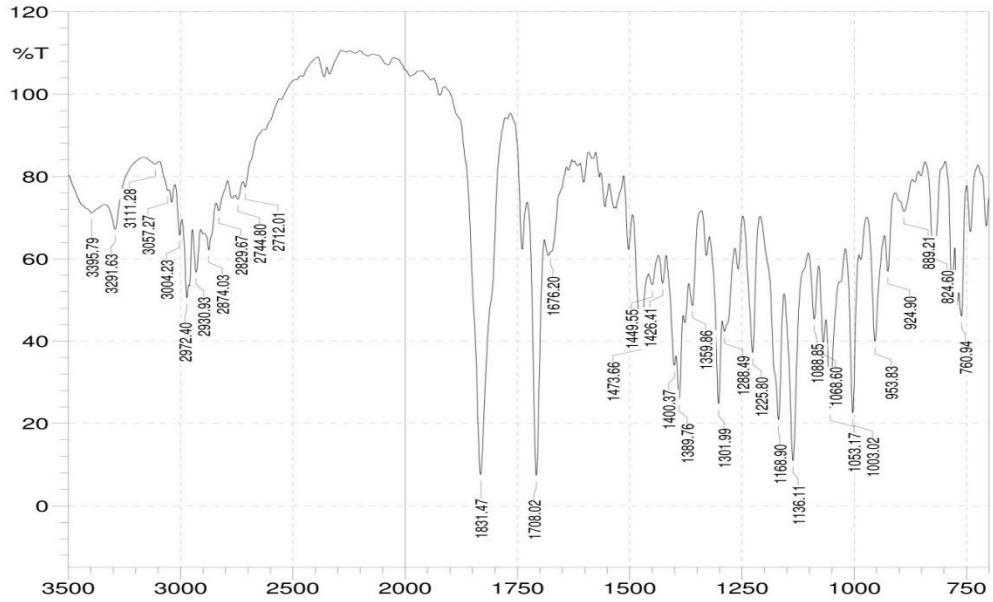


FIGURE 3l: FTIR SPECTRUM OF BEST FORMULATION (F1)

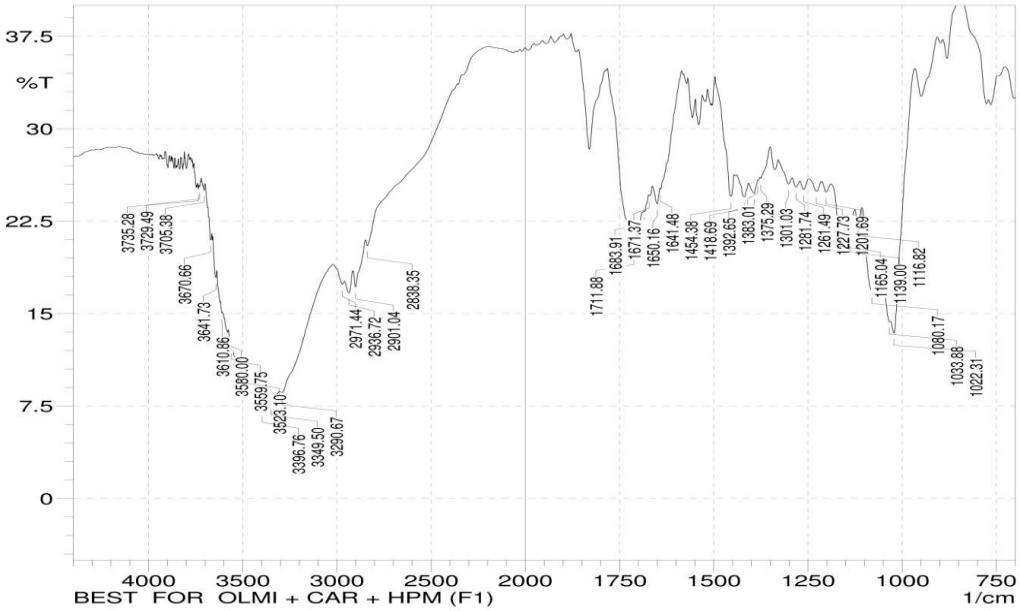


FIGURE 3m: DSC THERMOGRAM OF OLMESARTAN

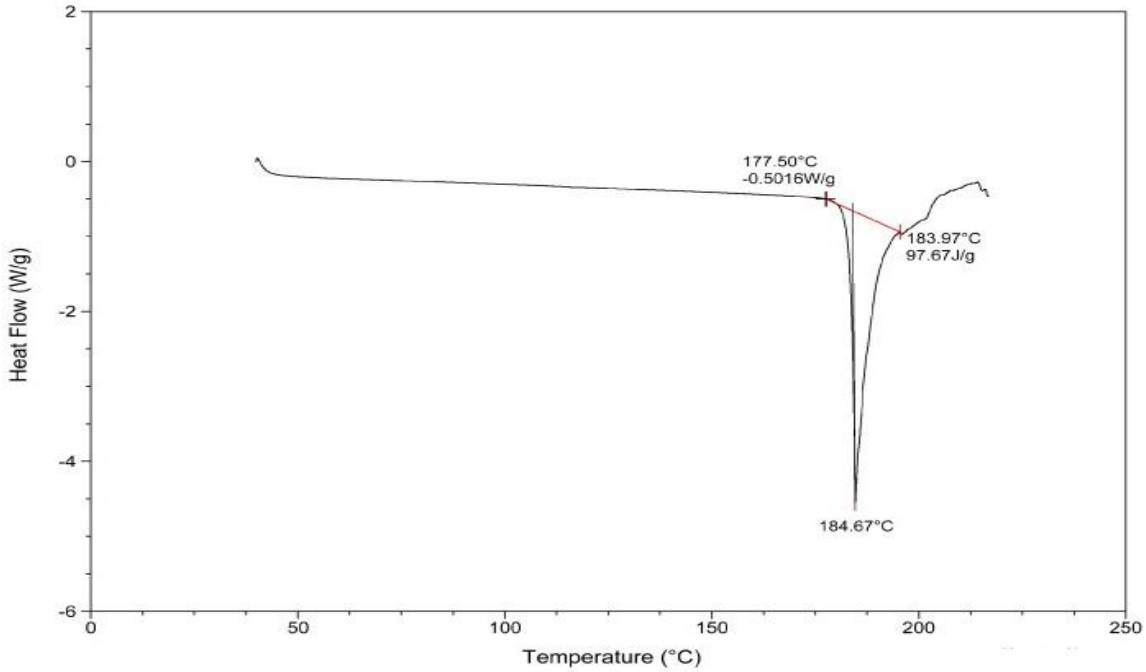


FIGURE 3n: DSC THERMOGRAM OF CARBOPOL 934P

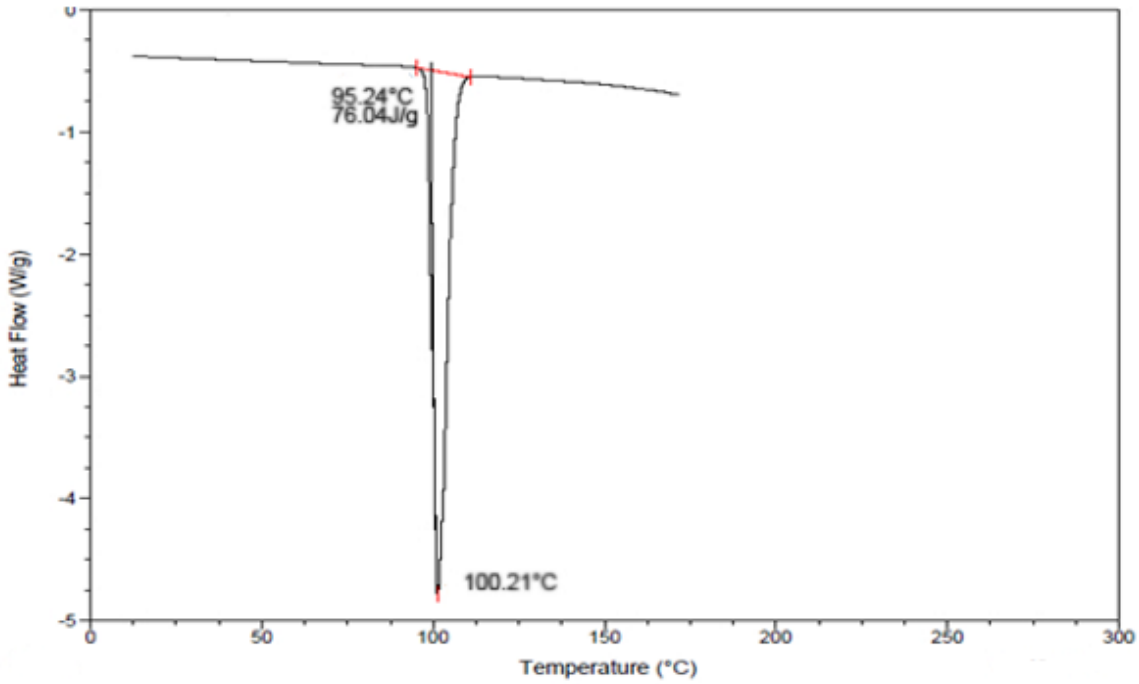


FIGURE 3p: DSC THERMOGRAM OF CHITOSAN

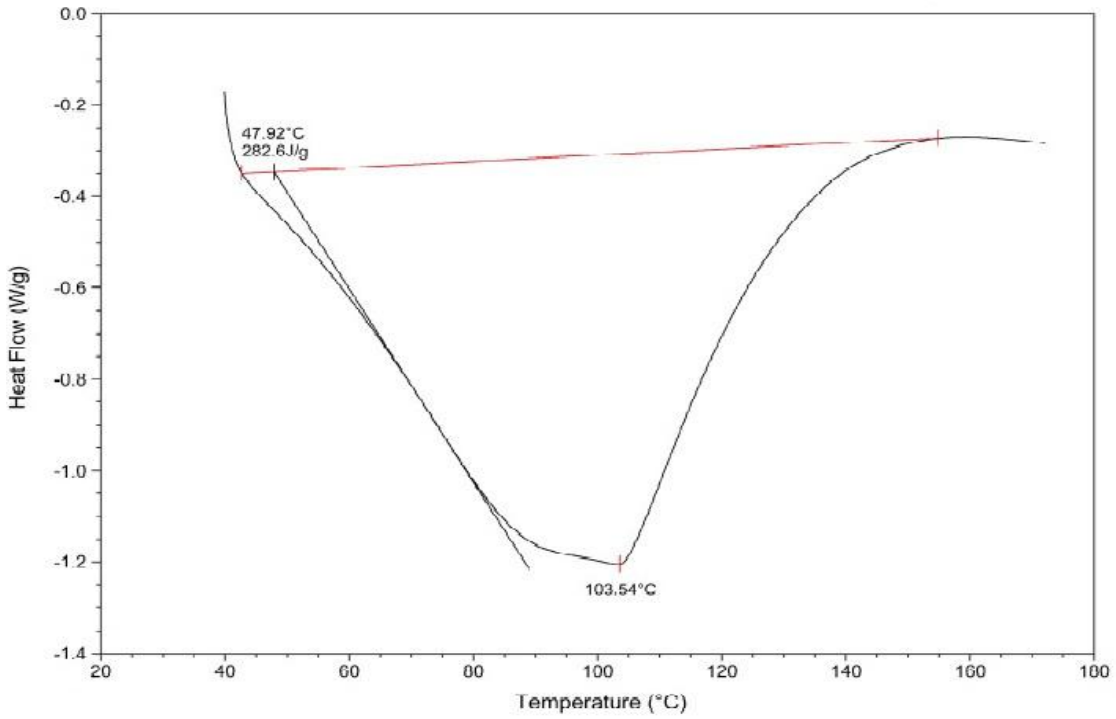


FIGURE 3q: DSC THERMOGRAM OF HPMC K15M

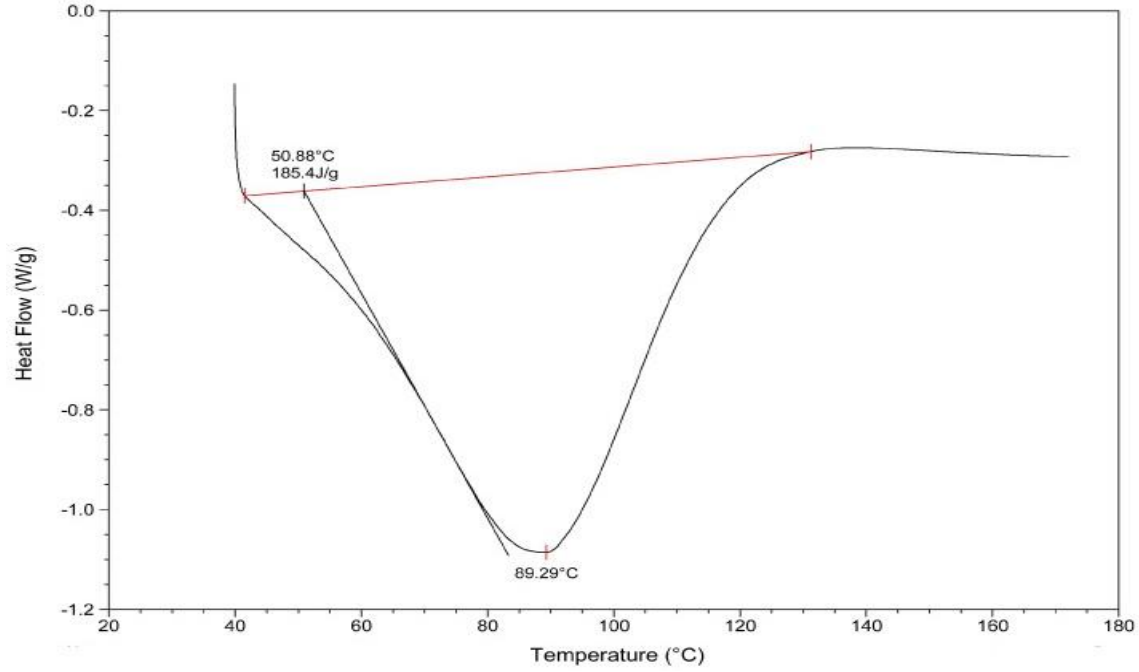


FIGURE 3r: DSC THERMOGRAM OF CMC SODIUM

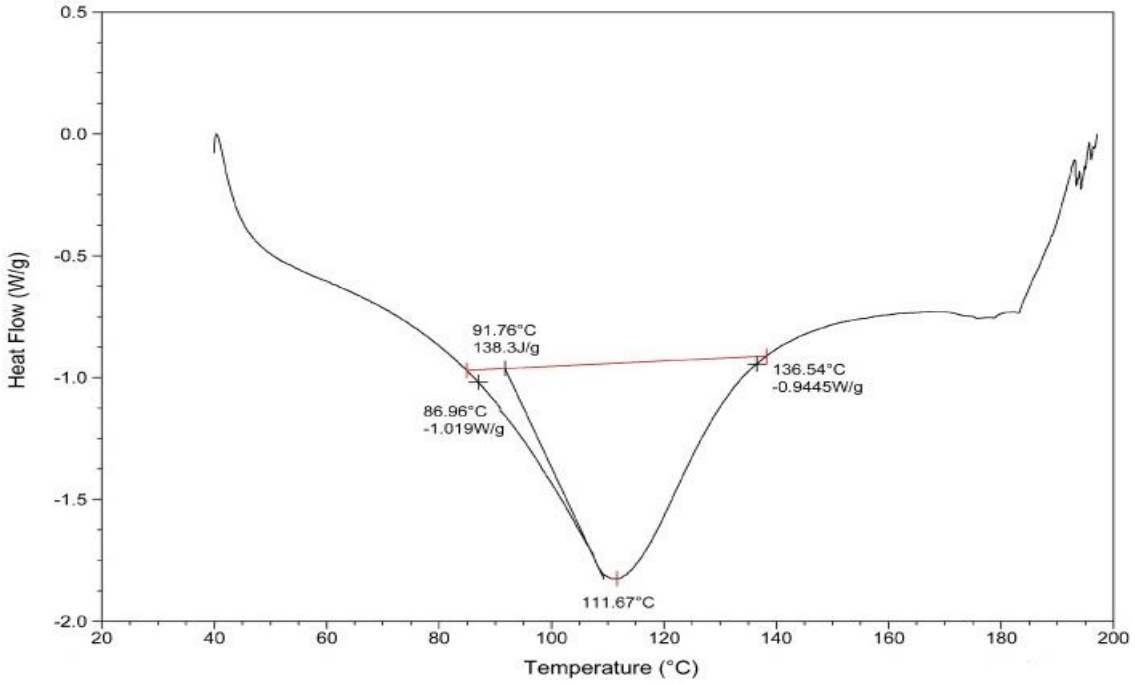


FIGURE 3s: DSC THERMOGRAM OF XANTHAN GUM

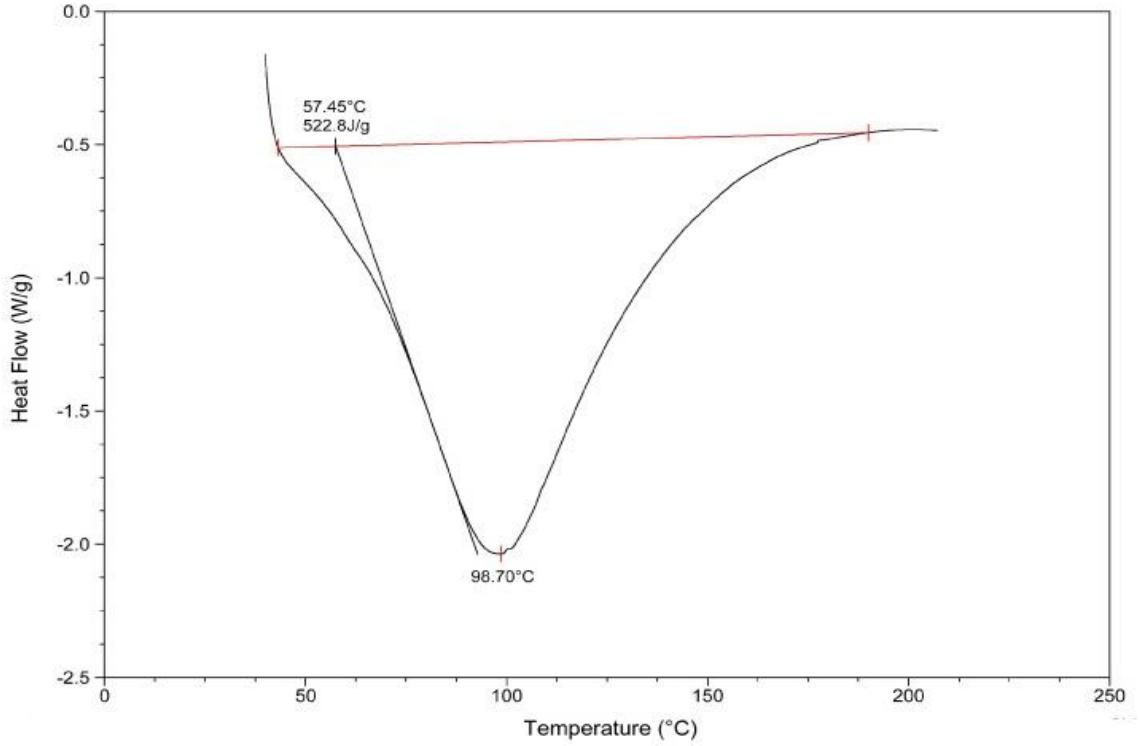


FIGURE 3t: DSC THERMOGRAM OF BEST FORMULATION (F1)

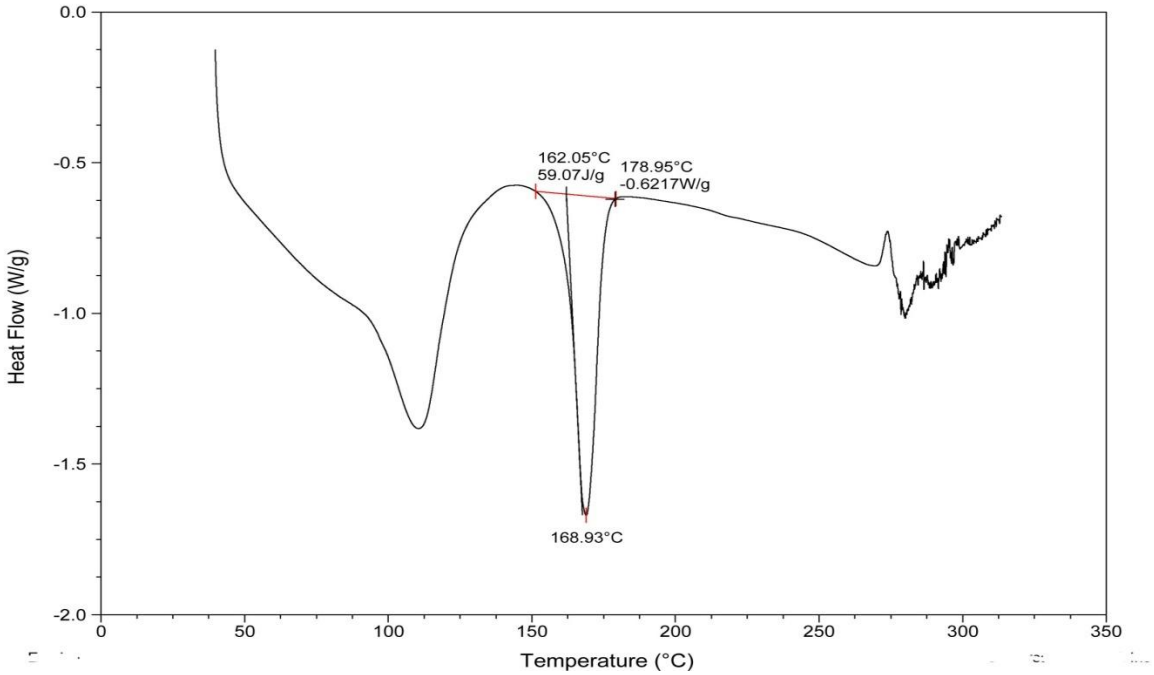


FIGURE 4: BULK DENSITY OF ALL THE FORMULATIONS

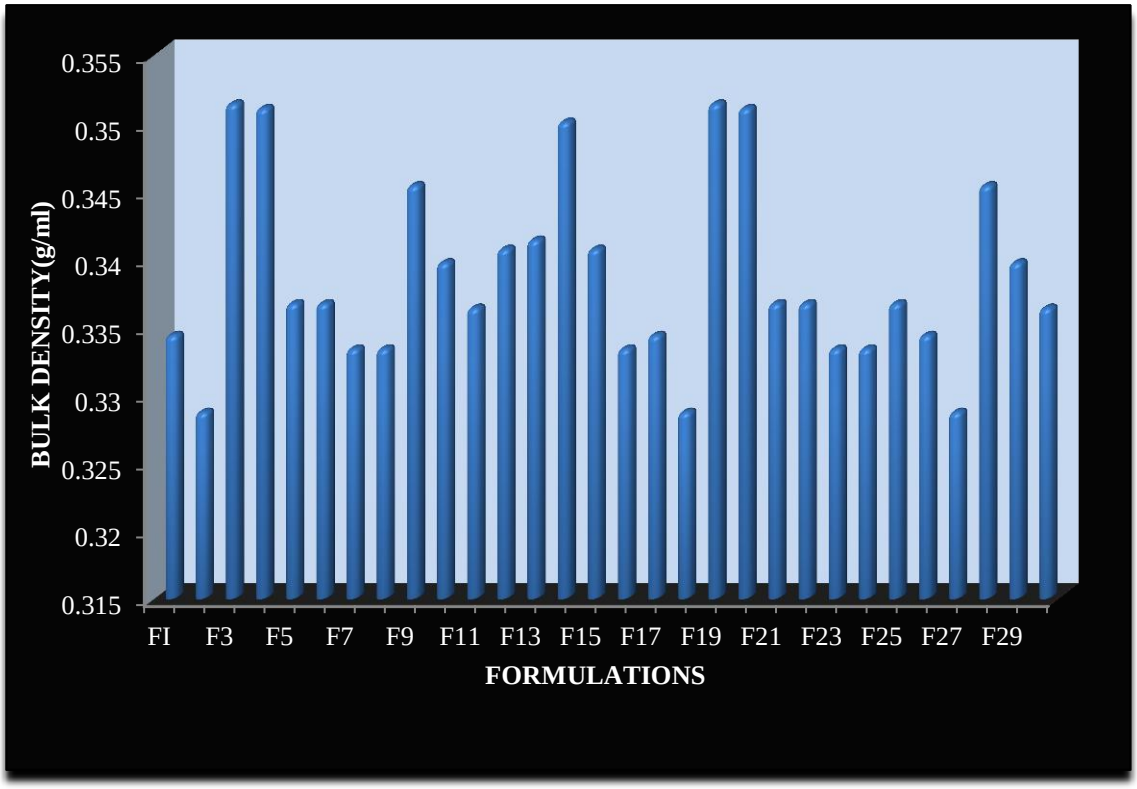


FIGURE 5: TAPPED DENSITY OF ALL THE FORMULATIONS

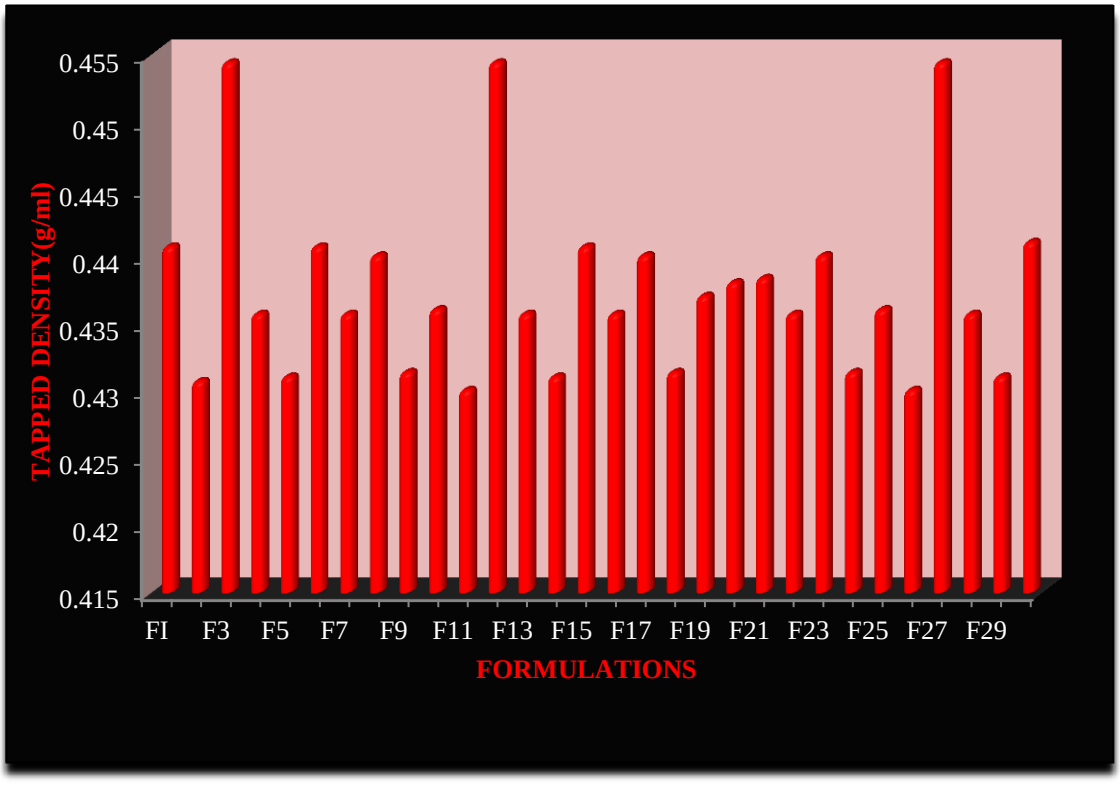


FIGURE 6: CARR'S INDEX OF ALL THE FORMULATIONS

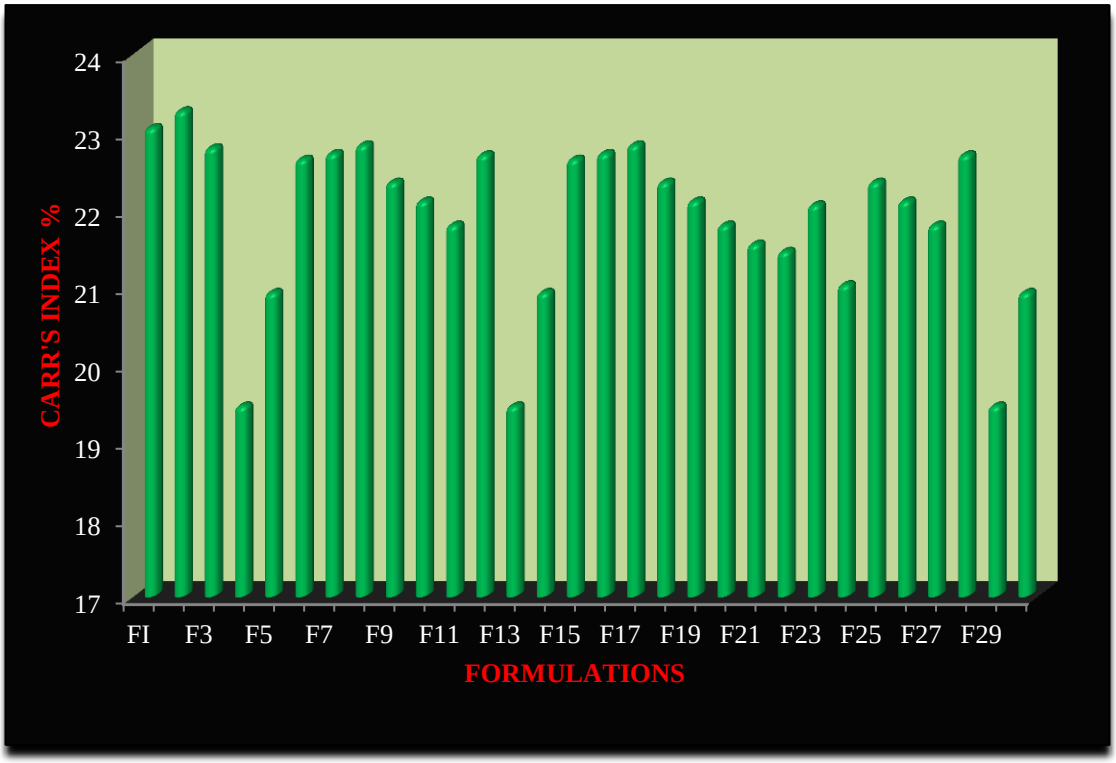


FIGURE 7: HAUSNER RATIO OF ALL THE FORMULATIONS

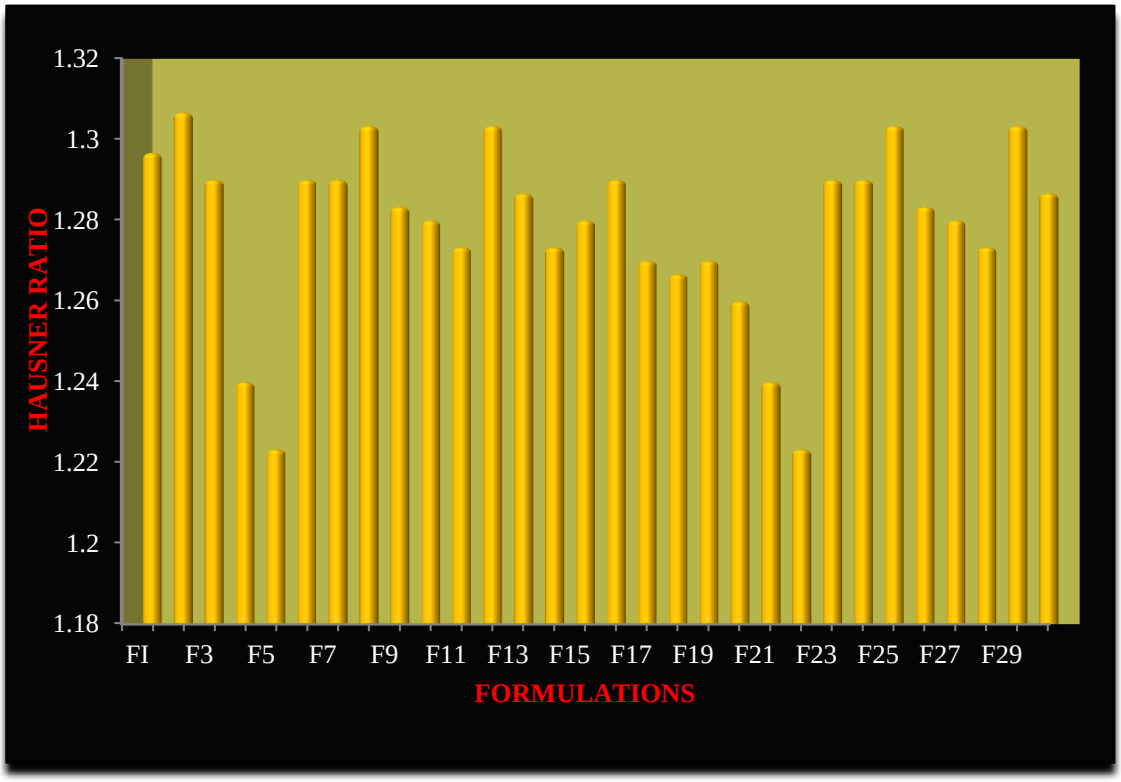


FIGURE 8: ANGLE OF REPOSE OF ALL THE FORMULATIONS

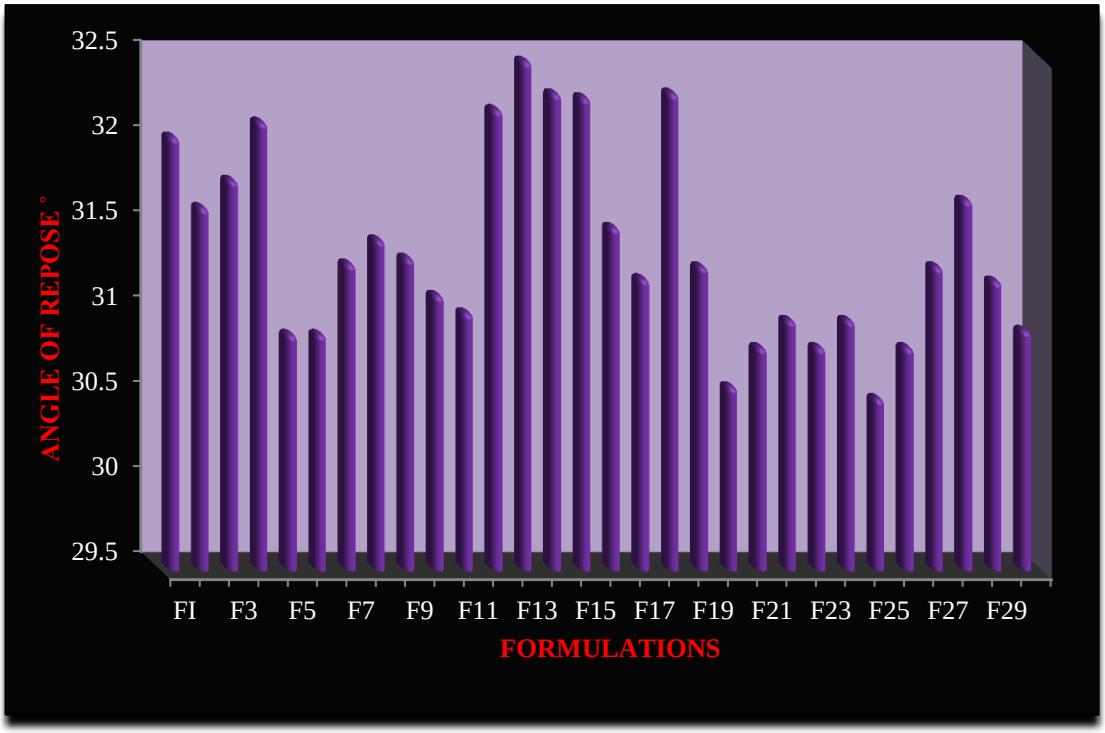


FIGURE 9a:MUCOADHESIVE STRENGTH OF BUCCAL ADHESIVE TABLETS(F1-F5)

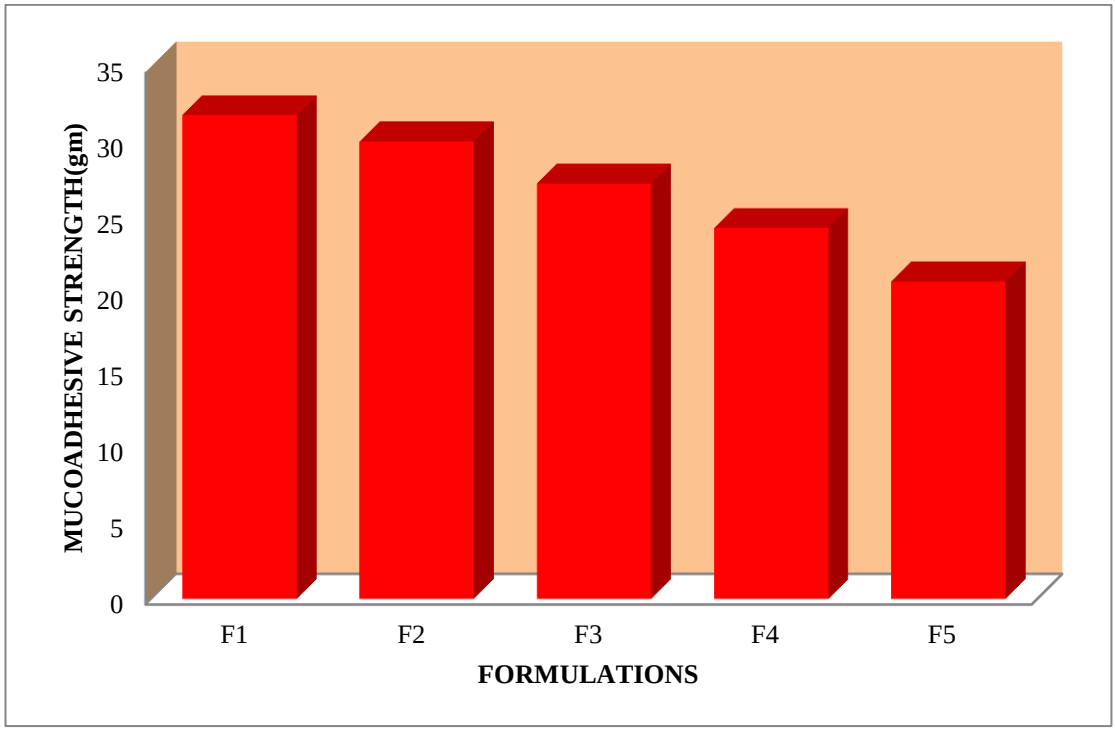


FIGURE 9b: MUCOADHESIVE STRENGTH OF BUCCAL ADHESIVE TABLETS (F6-F10)

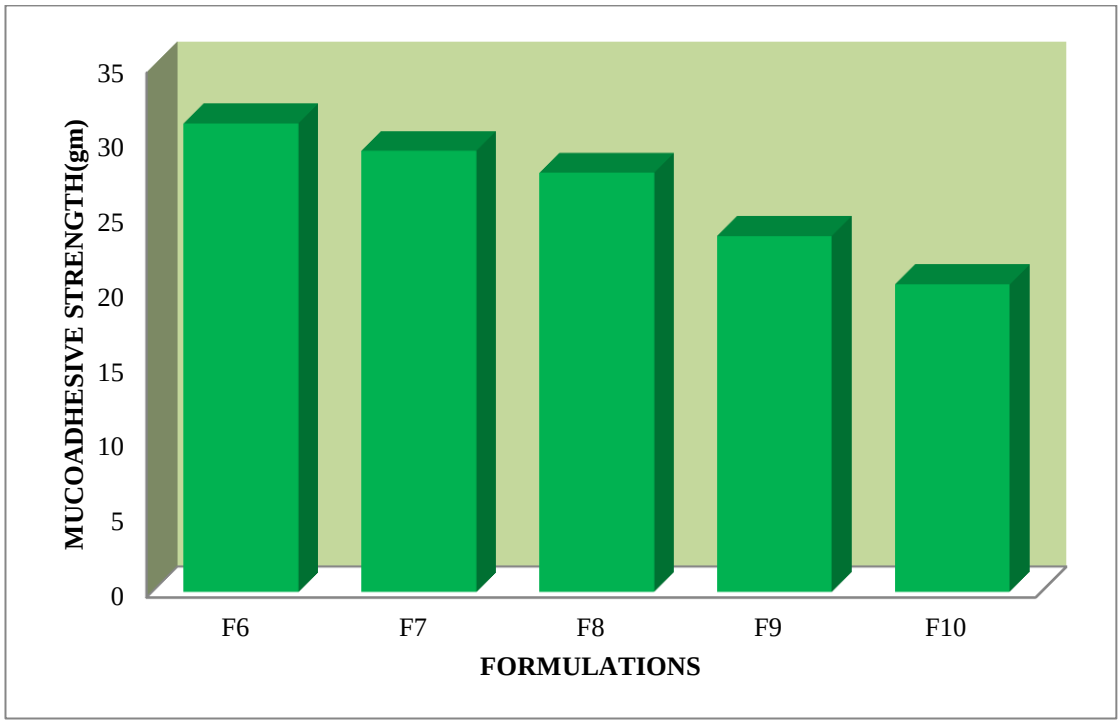


FIGURE 9c: MUCOADHESIVE STRENGTH OF BUCCAL ADHESIVE TABLETS (F11-F15)

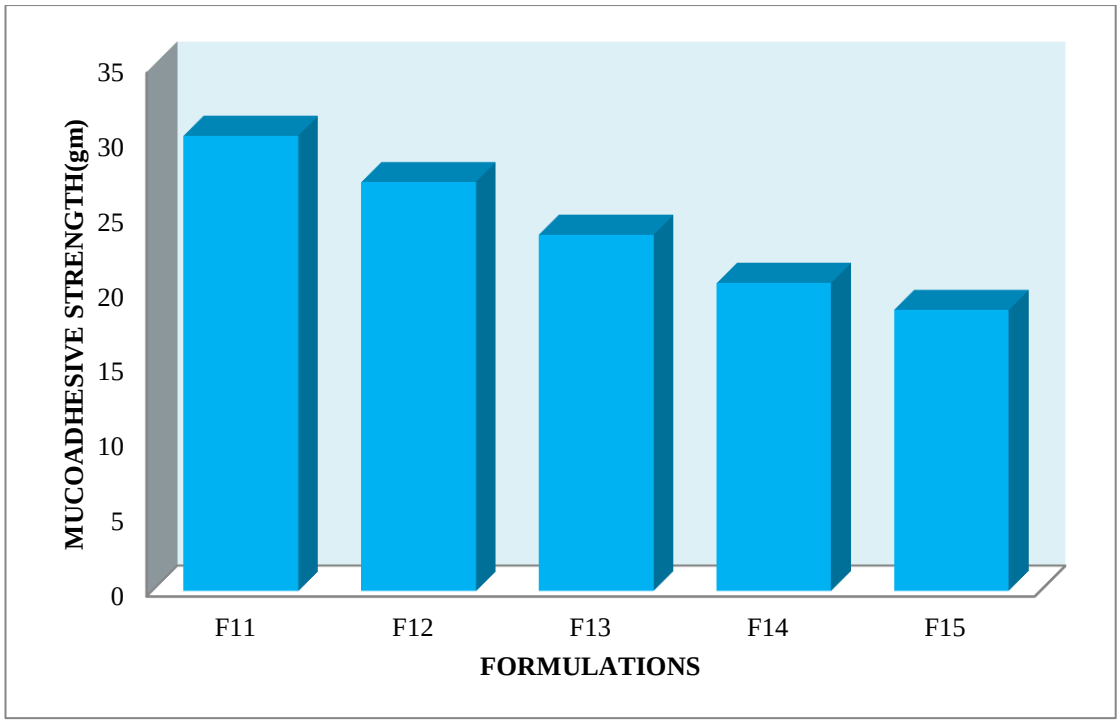


FIGURE 9d: MUCOADHESIVE STRENGTH OF BUCCAL ADHESIVE TABLETS (F16-F20)

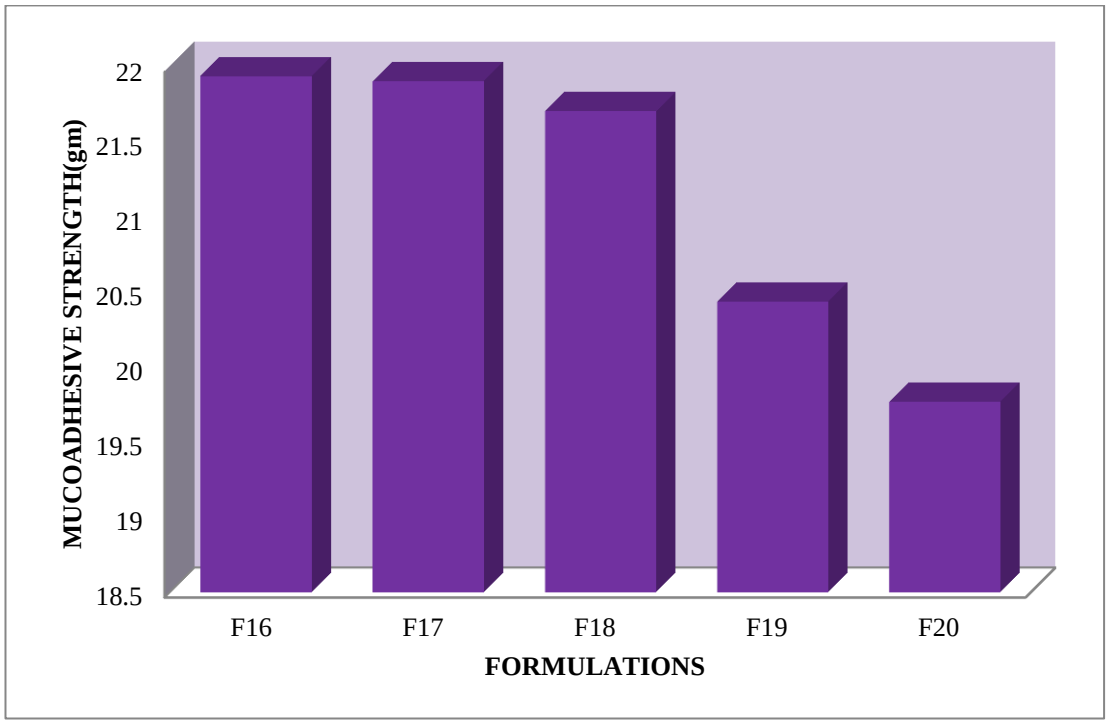


FIGURE 9e: MUCOADHESIVE STRENGTH OF BUCCAL ADHESIVE TABLETS (F21-F25)

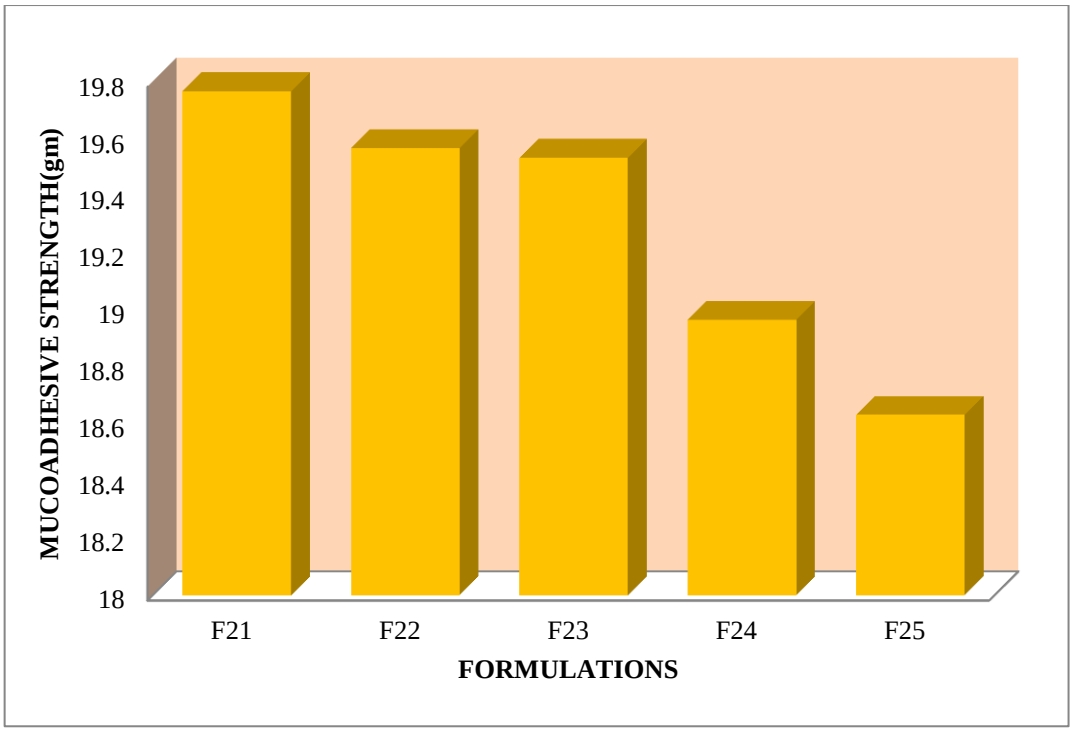


FIGURE 9f: MUCOADHESIVE STRENGTH OF BUCCAL ADHESIVE TABLETS (F26-F30)

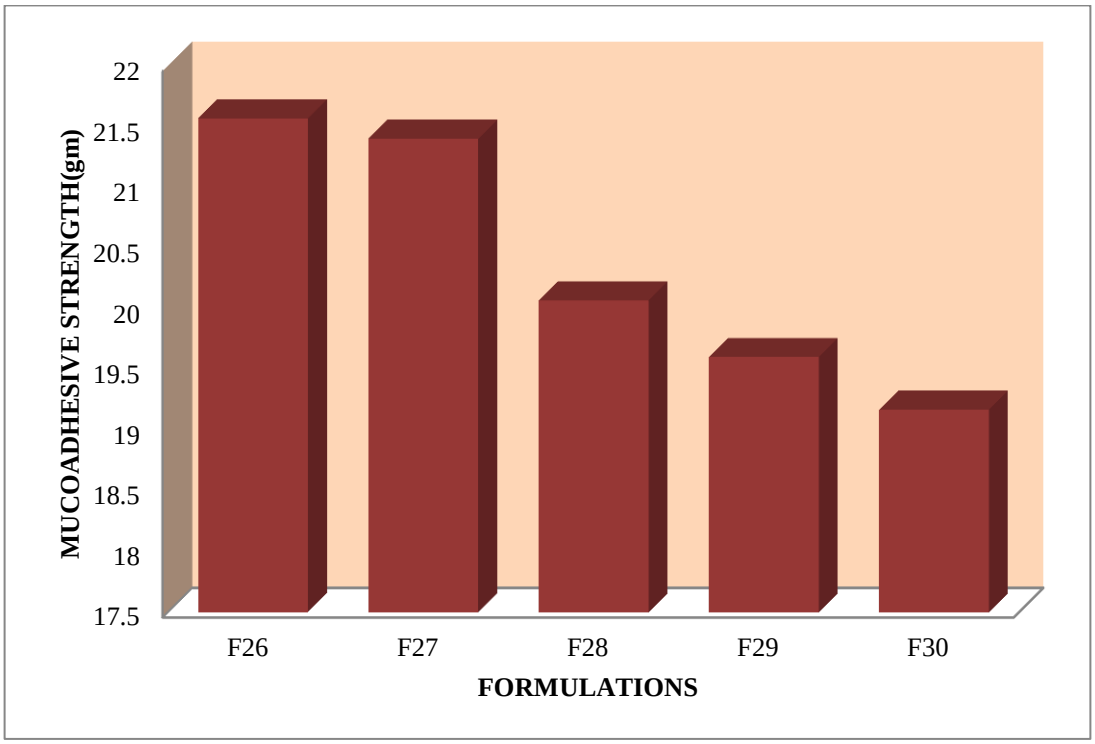


FIGURE 10a: SWELLING INDEX OF BUCCAL ADHESIVE TABLETS (F1-F5)

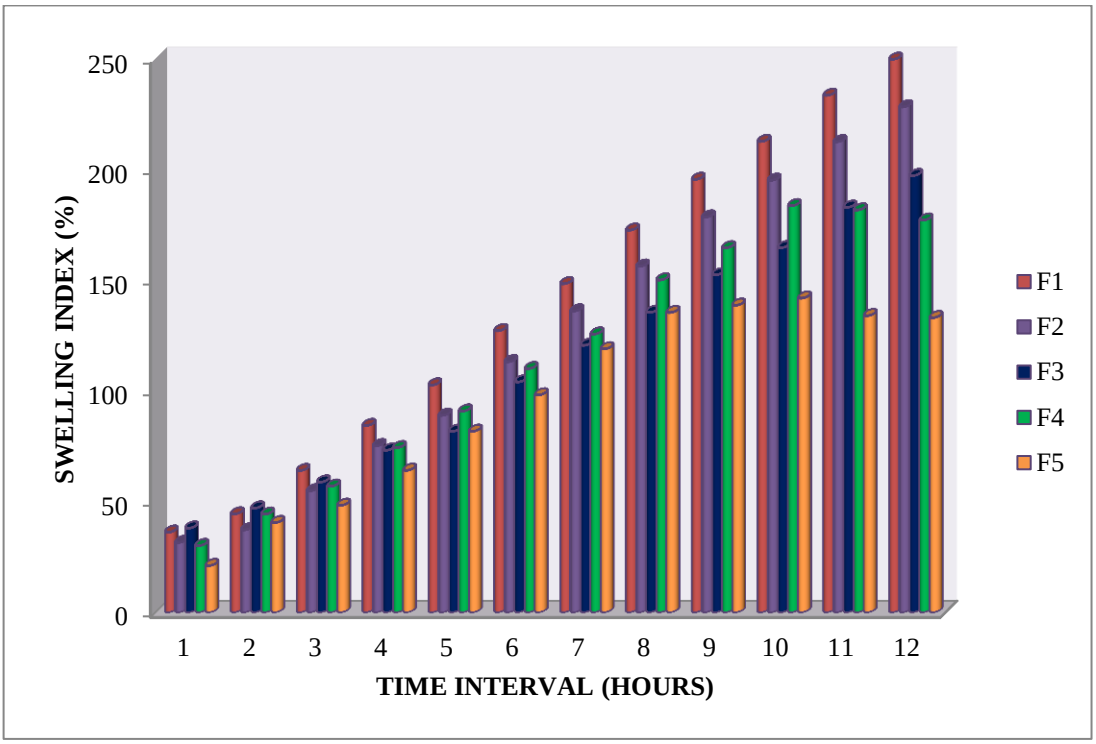


FIGURE 10b: SWELLING INDEX OF BUCCAL ADHESIVE TABLETS (F6-F10)

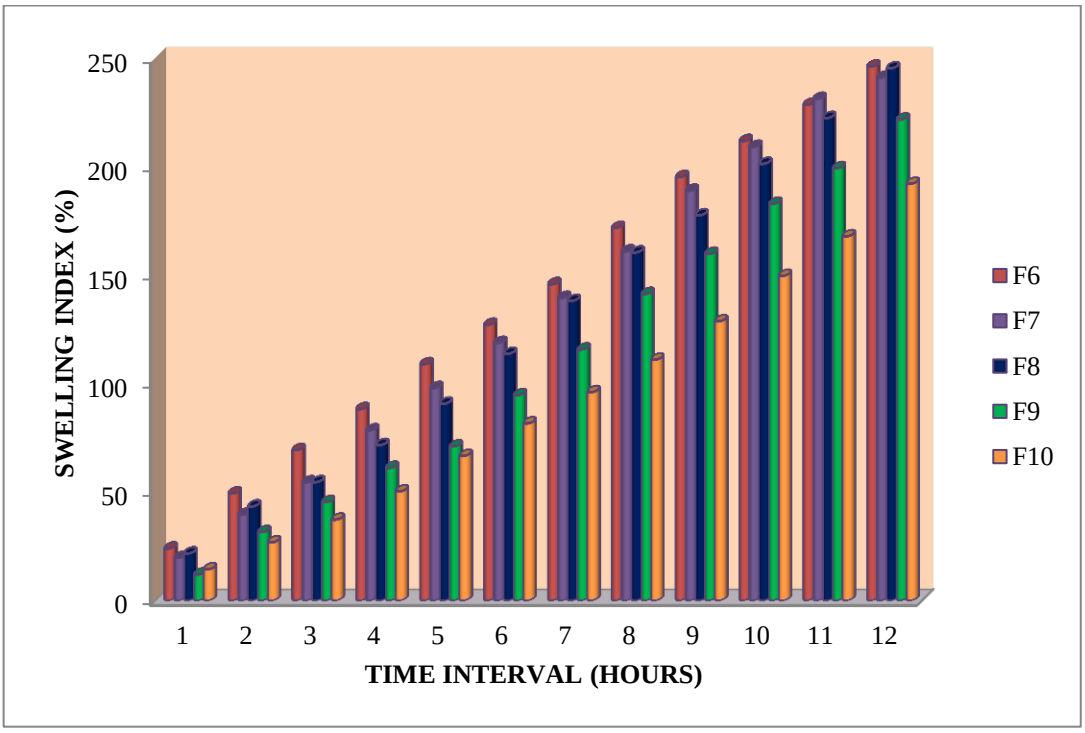


FIGURE 10c: SWELLING INDEX OF BUCCAL ADHESIVE TABLETS (F11-F15)

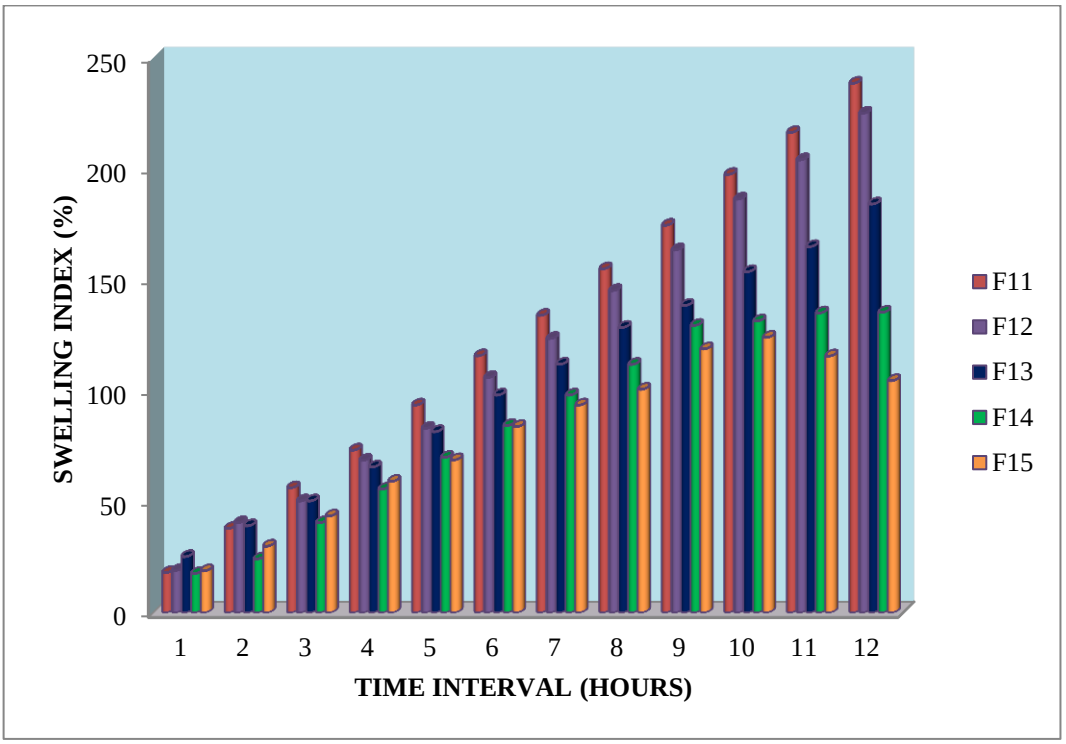


FIGURE 10d: SWELLING INDEX OF BUCCAL ADHESIVE TABLETS (F16-F20)

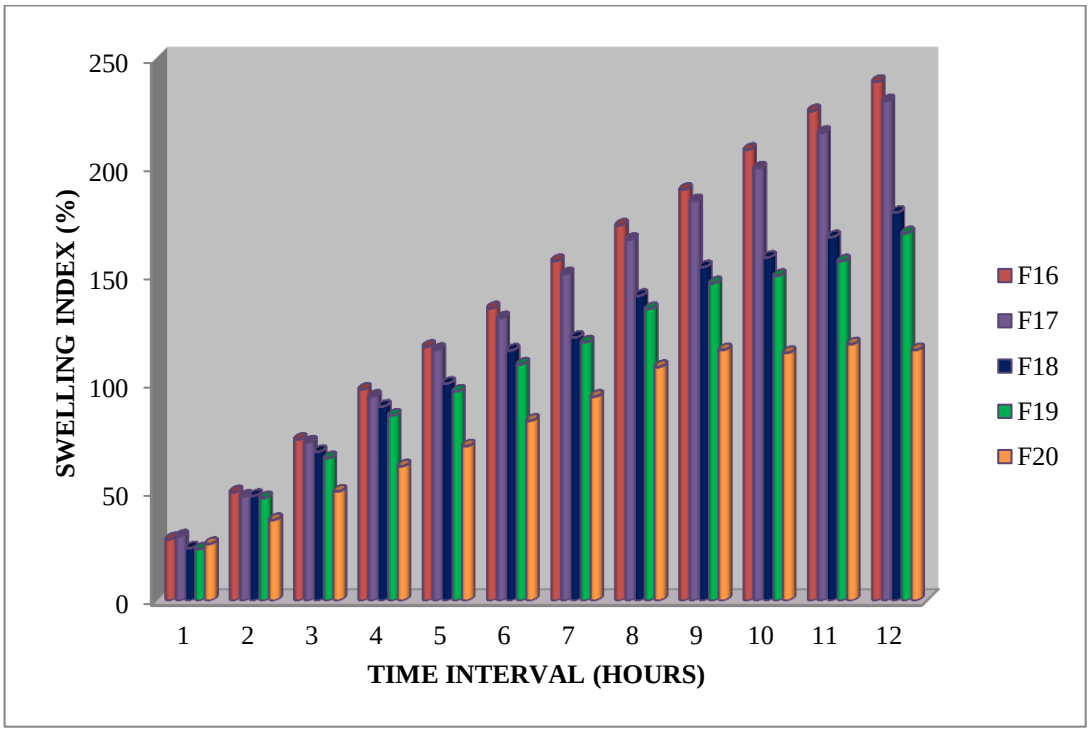


FIGURE 10e: SWELLING INDEX OF BUCCAL ADHESIVE TABLETS (F21-F25)

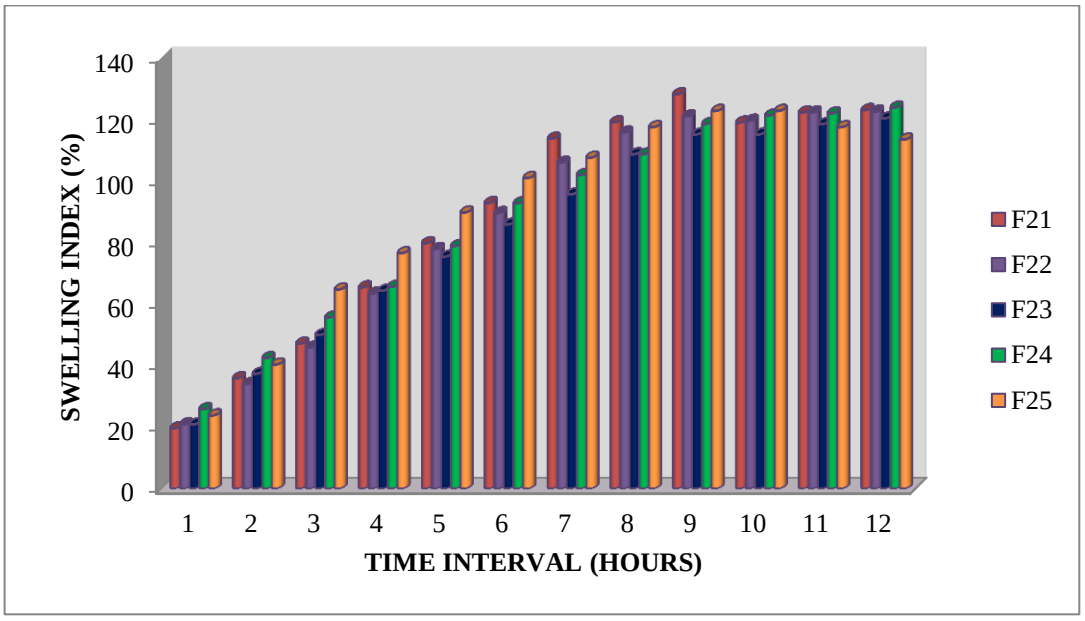


FIGURE 10f: SWELLING INDEX OF BUCCAL ADHESIVE TABLETS (F26-F30)

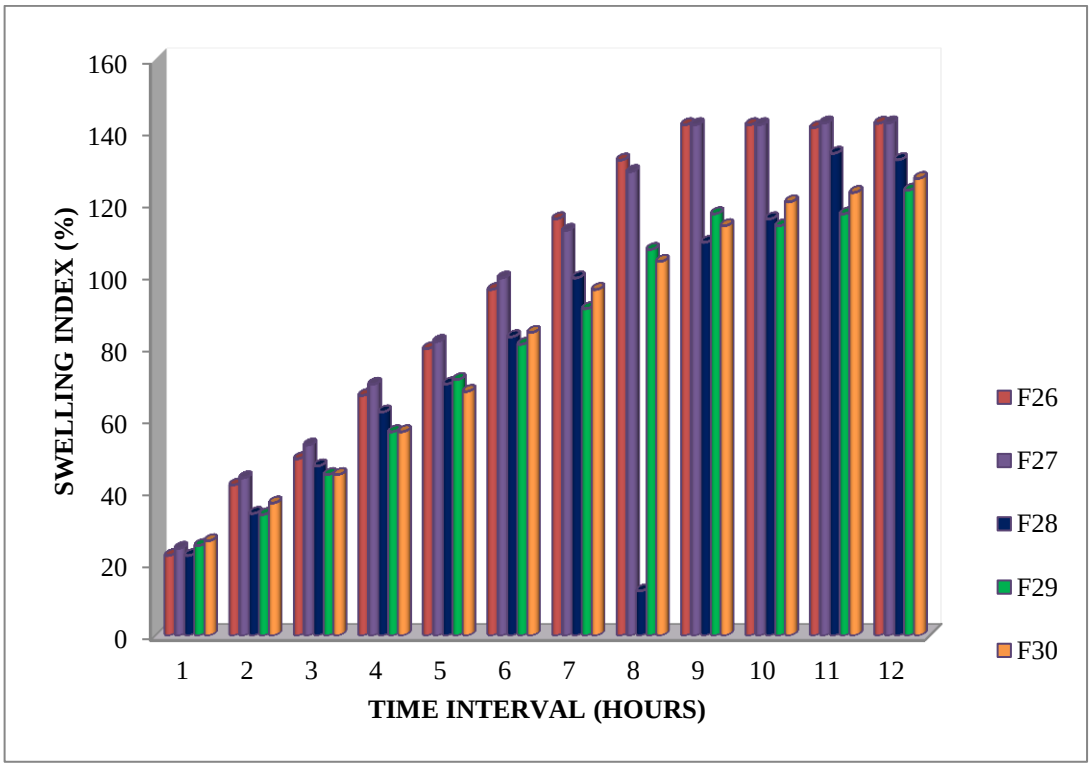


FIGURE 11a: INVITRO DISSOLUTION STUDIES OF OLMESARTAN BUCCAL ADHESIVE TABLETS (CARBOPOL: HPMC K15M)

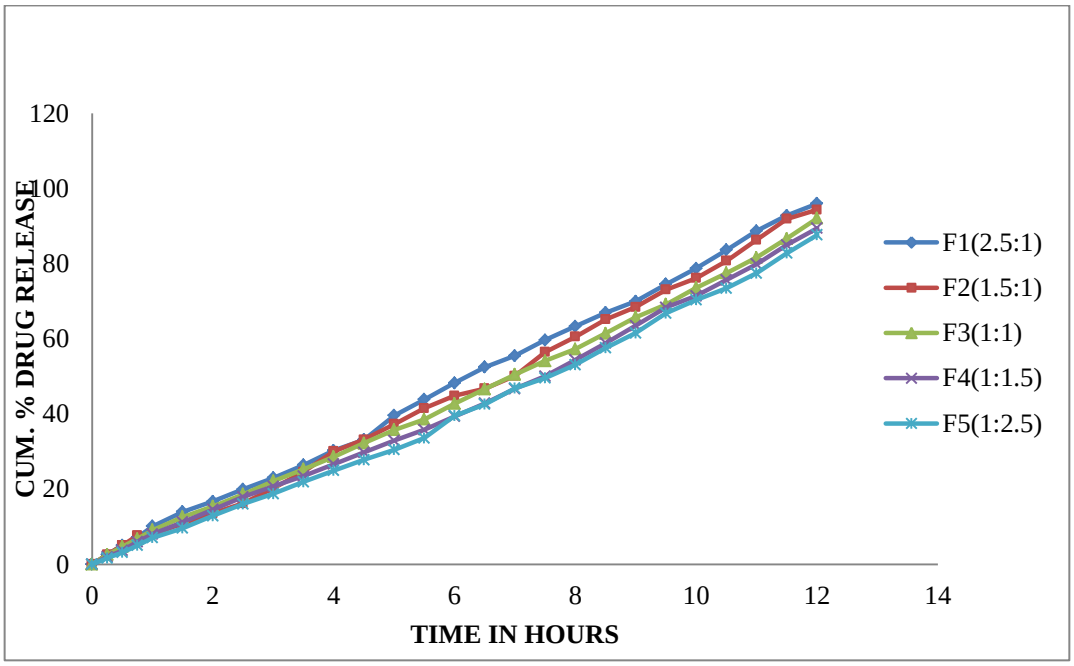


FIGURE 11b: INVITRO DISSOLUTION STUDIES OF OLMESARTAN BUCCAL ADHESIVE TABLETS (Carbopol934: Xanthan Gum)

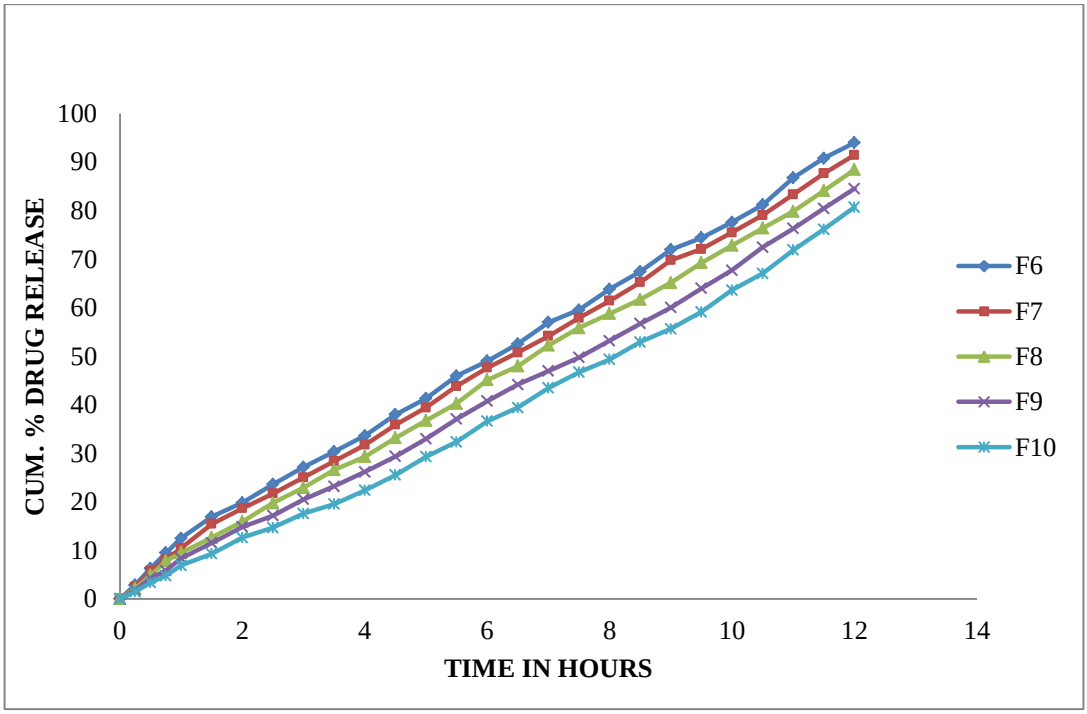


FIGURE 11c: INVITRO DISSOLUTION STUDIES OF OLMESARTAN BUCCAL ADHESIVE TABLETS(CARBOPOL:CMC SODIUM)

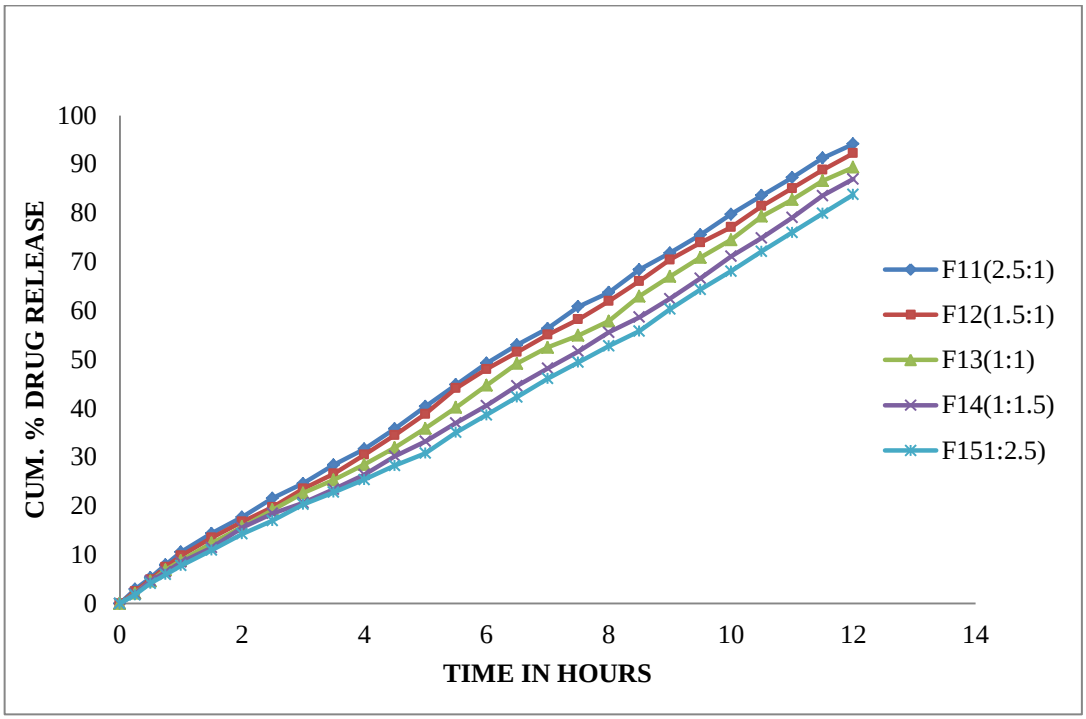


FIGURE 11d: INVITRO DISSOLUTION STUDIES OF OLMESARTAN BUCCAL ADHESIVE TABLETS(CARBOPOL:CHITOSAN)

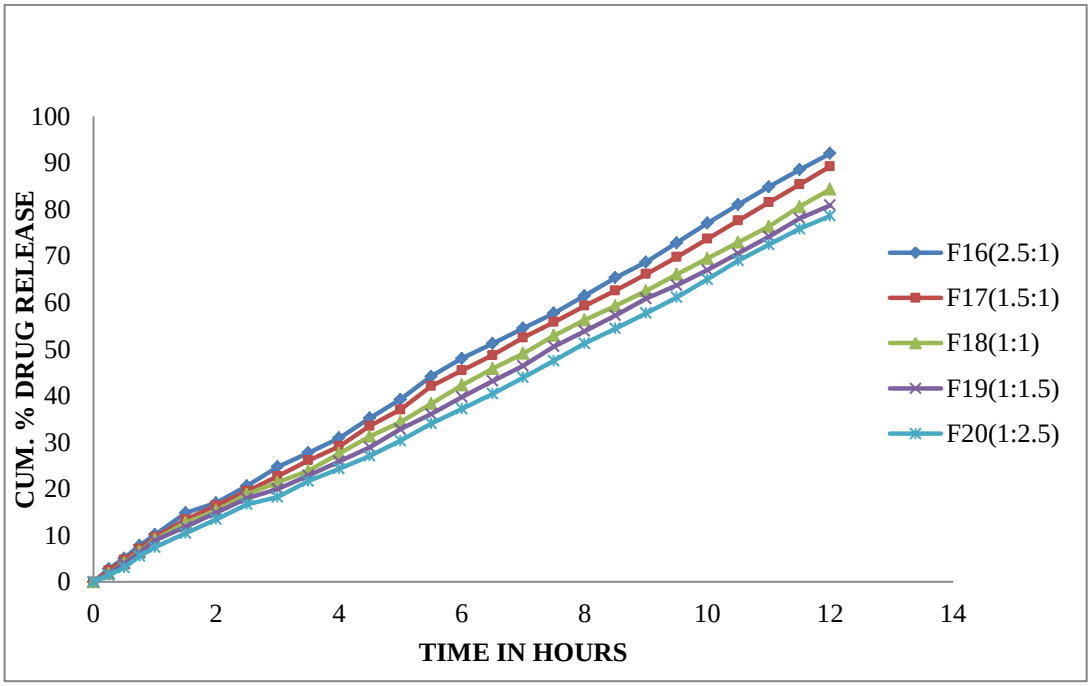


FIGURE 11e: INVITRO DISSOLUTION STUDIES OF OLMESARTAN BUCCAL ADHESIVE TABLETS (HPMC K15M: CMC SODIUM)

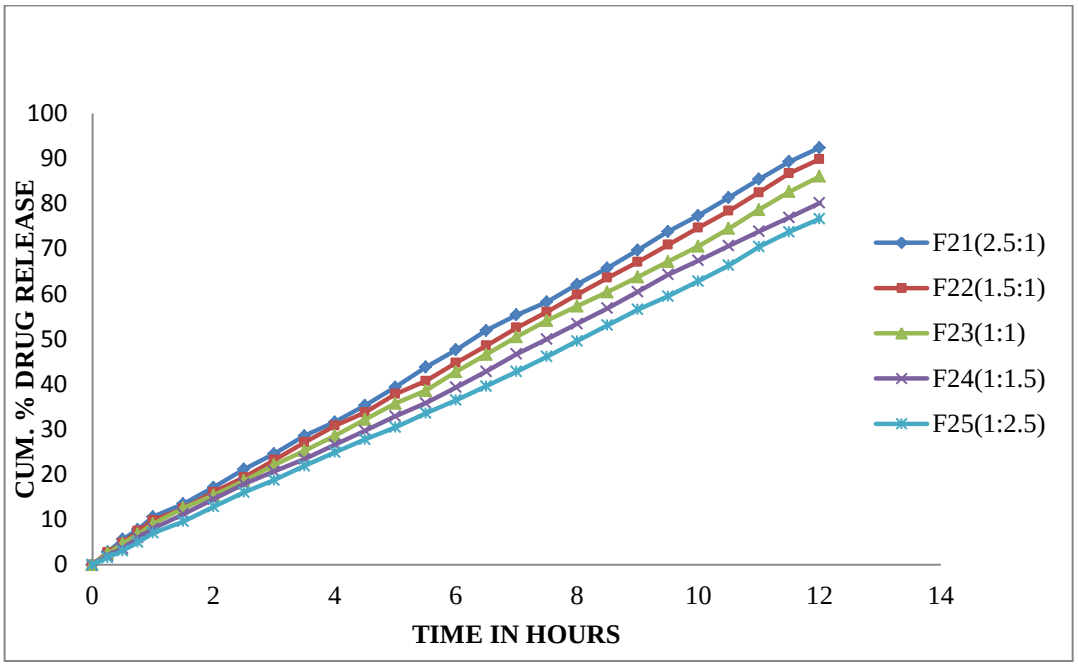


FIGURE 11f: INVITRO DISSOLUTION STUDIES OF OLMESARTAN BUCCAL ADHESIVE TABLETS(HPMC K15M:XANTHAN GUM)

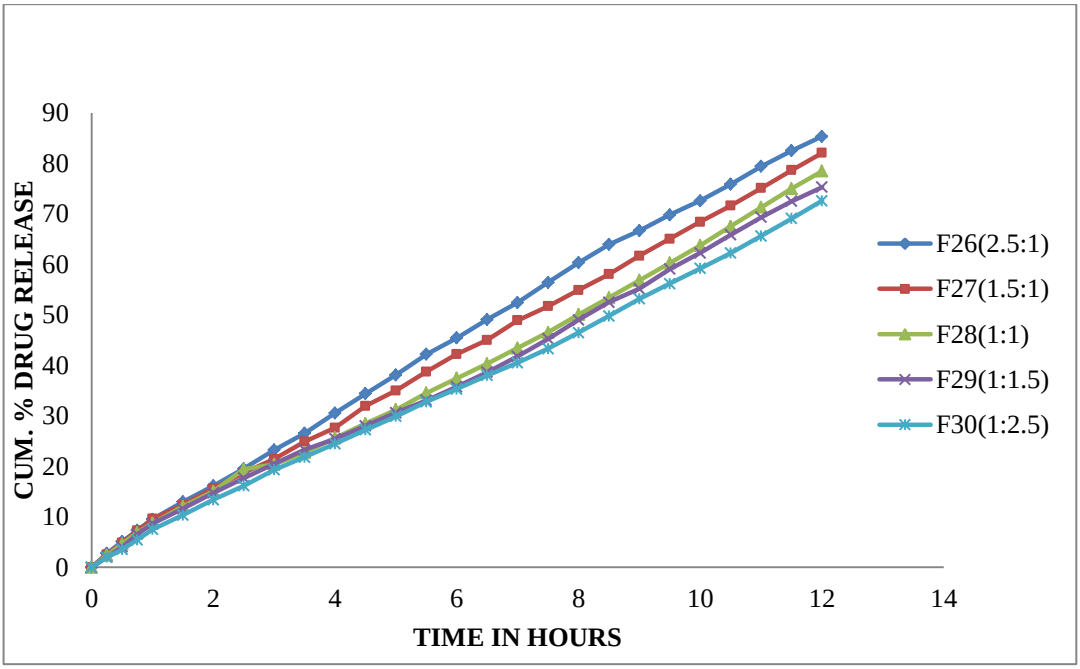


FIGURE 12a: COMPARISON OF ZERO ORDER RELEASE KINETICS OF FORMULATION CONTAINING CARBOPOL AND HPMC K15M IN DIFFERENT RATIOS

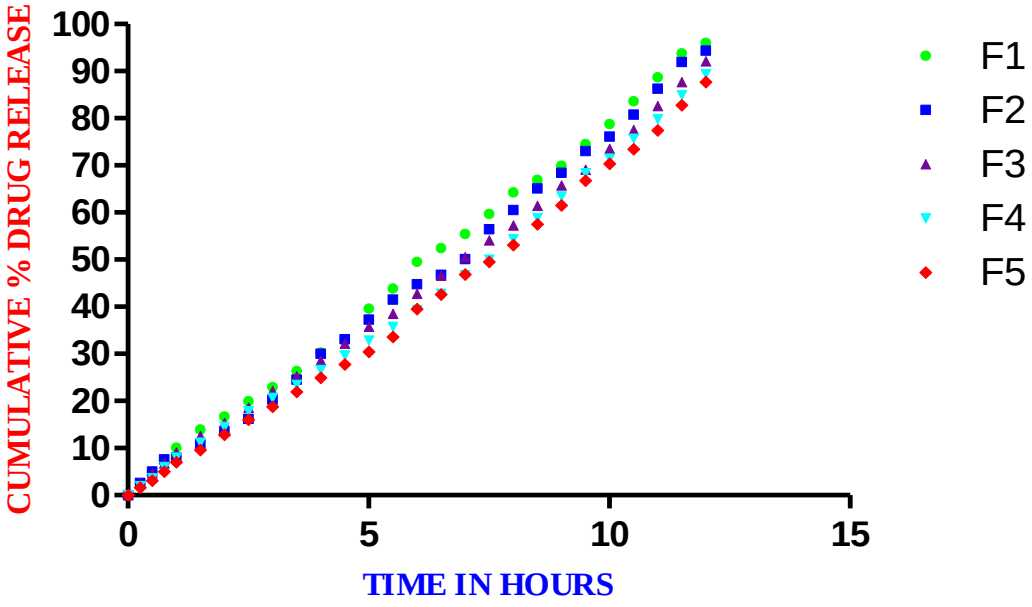


FIGURE 12b: COMPARISON OF ZERO ORDER RELEASE KINETICS OF FORMULATION CONTAINING CARBOPOL AND XANTAHN GUM IN DIFFERENT RATIOS

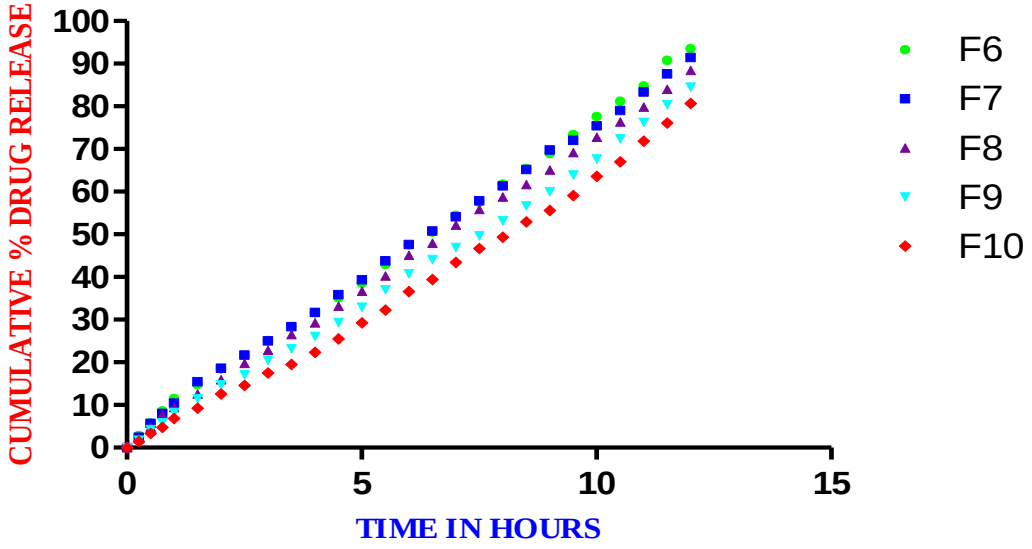


FIGURE 12C: COMPARISON OF ZERO ORDER RELEASE KINETICS OF FORMULATION CONTAINING CARBOPOL AND CMC SODIUM IN DIFFERENT RATIOS

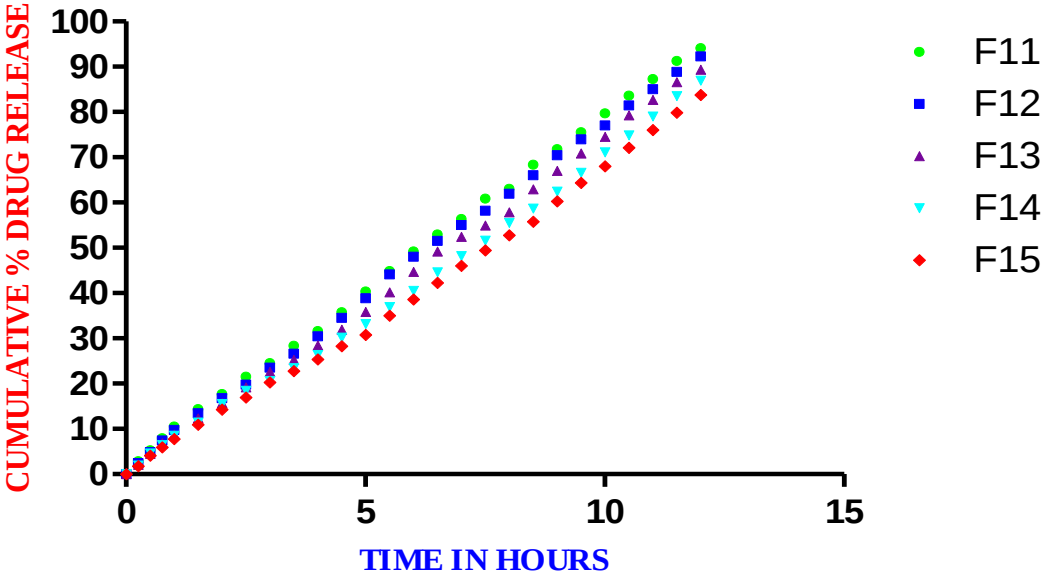


FIGURE 12d: COMPARISON OF ZERO ORDER RELEASE KINETICS OF FORMULATION CONTAINING CARBOPOL AND CHITOSAN IN DIFFERENT RATIOS

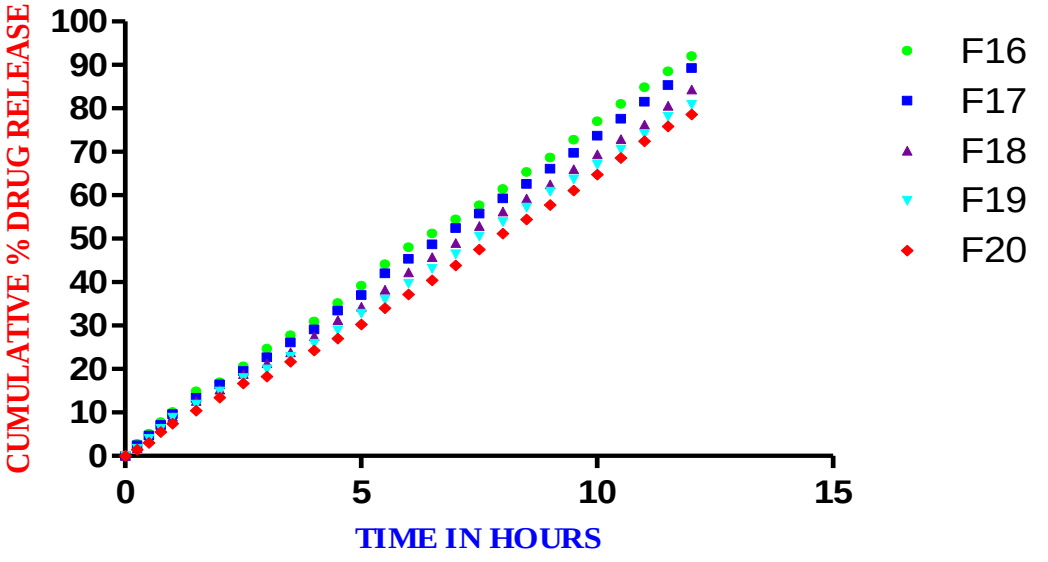


FIGURE 12e: COMPARISON OF ZERO ORDER RELEASE KINETICS OF FORMULATION CONTAINING HPMC K15M AND CMC SODIUM IN DIFFERENT RATIOS

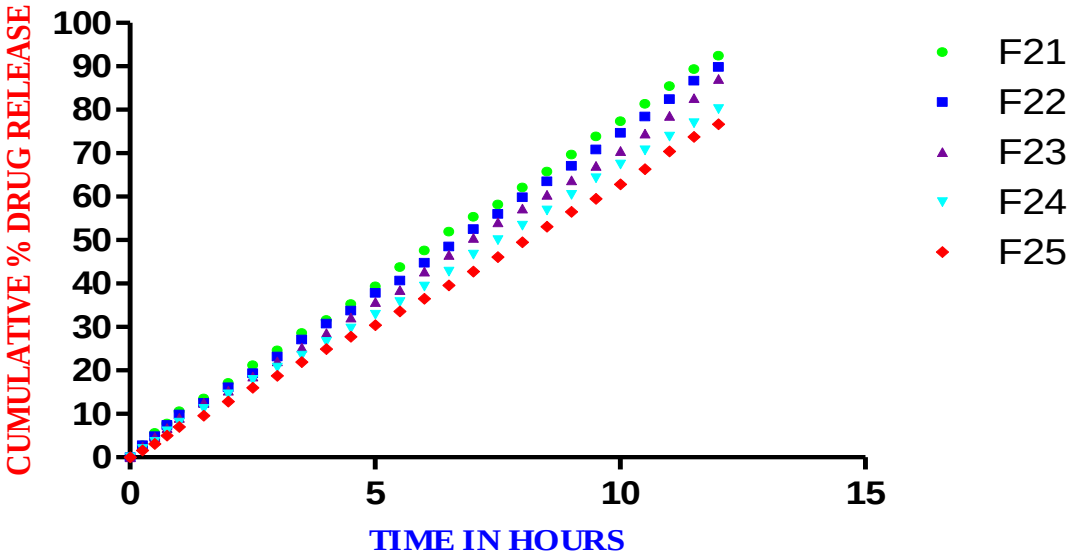


FIGURE 12f: COMPARISON OF ZERO ORDER RELEASE KINETICS OF FORMULATION CONTAINING HPMC K15M AND XANTHAN GUM IN DIFFERENT RATIOS

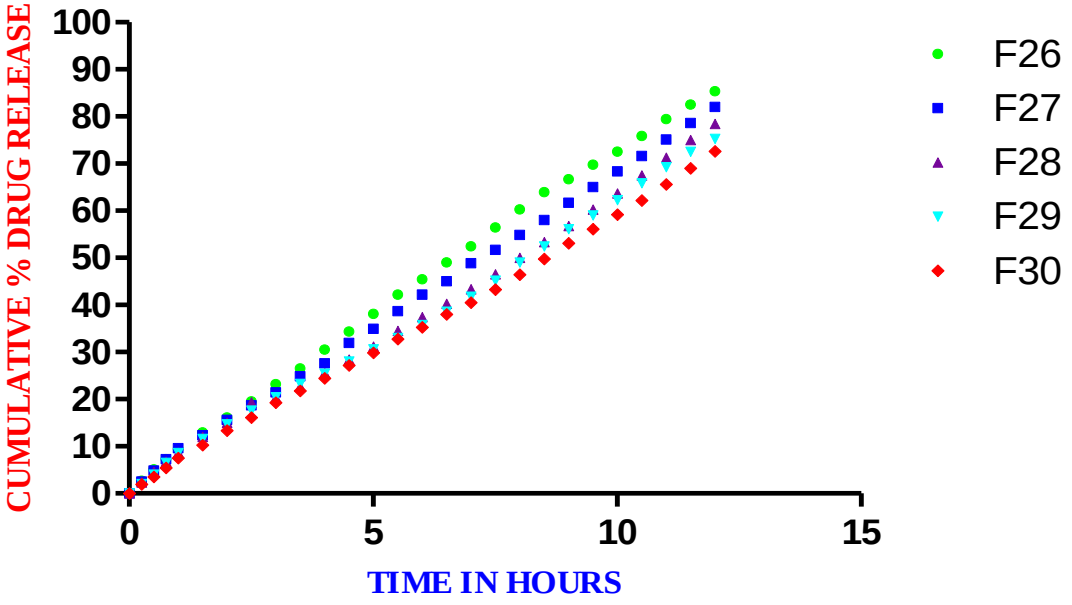


FIGURE 13a: COMPARISON OF FIRST ORDER RELEASE KINETICS OF FORMULATION CONTAINING CARBOPOL AND HPMC K15M IN DIFFERENT RATIOS

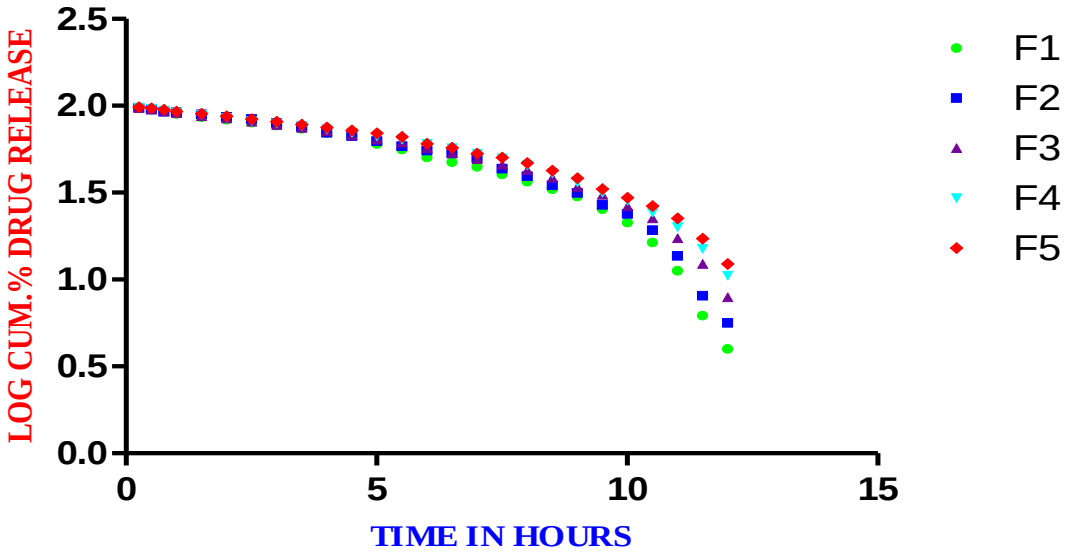


FIGURE 13b: COMPARISON OF FIRST ORDER RELEASE KINETICS OF FORMULATION CONTAINING CARBOPOL AND XANTHAN GUM IN DIFFERENT RATIOS

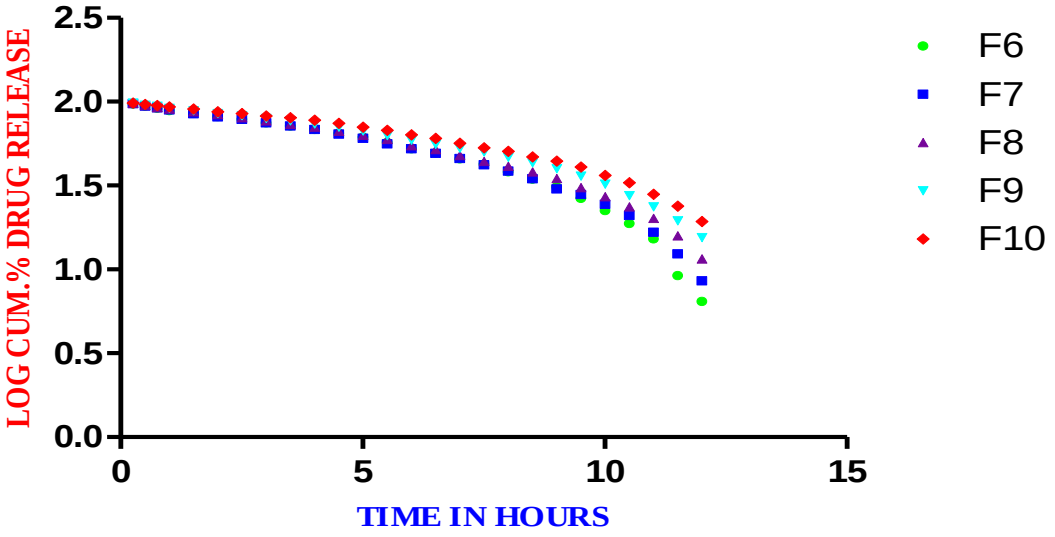


FIGURE 13c: COMPARISON OF FIRST ORDER RELEASE KINETICS OF FORMULATION CONTAINING CARBOPOL AND CMC SODIUM IN DIFFERENT RATIOS

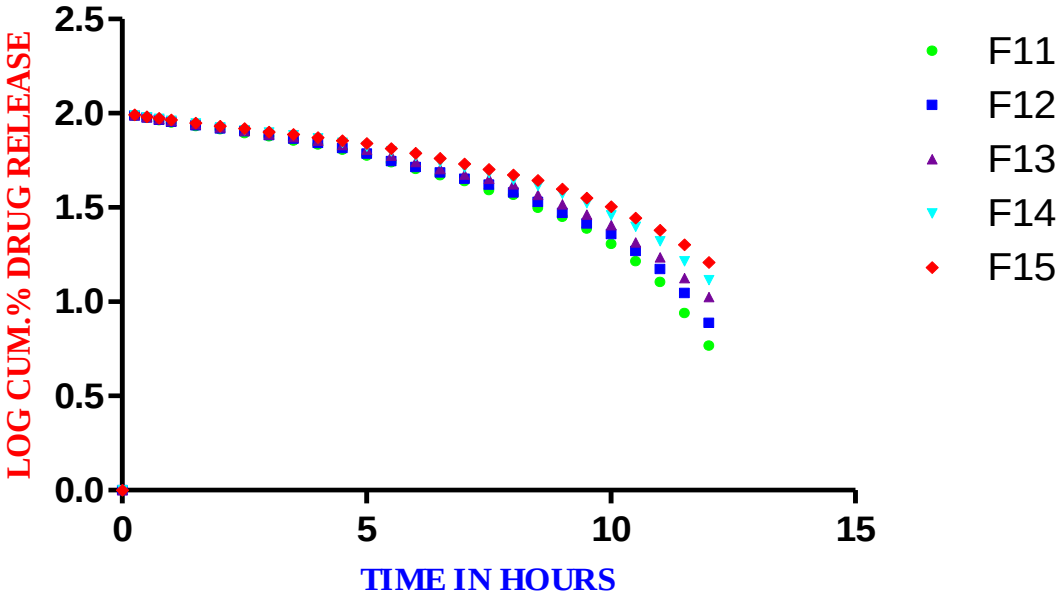


FIGURE 13d: COMPARISON OF FIRST ORDER RELEASE KINETICS OF FORMULATION CONTAINING CARBOPOL AND CHITOSAN IN DIFFERENT RATIOS

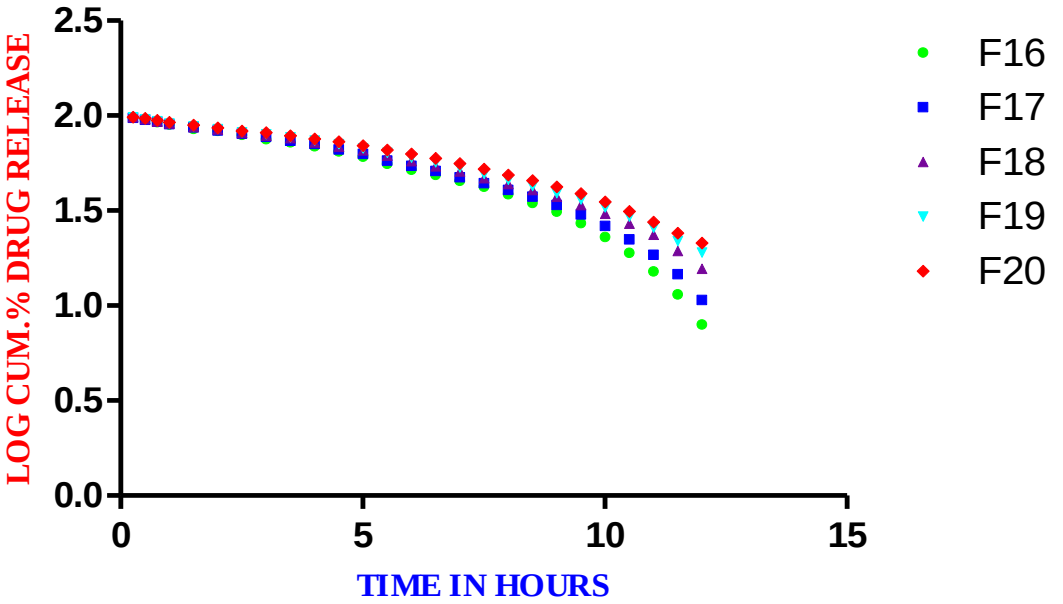


FIGURE 13e: COMPARISON OF FIRST ORDER RELEASE KINETICS OF FORMULATION CONTAINING HPMC K15M AND CMC SODIUM IN DIFFERENT RATIOS

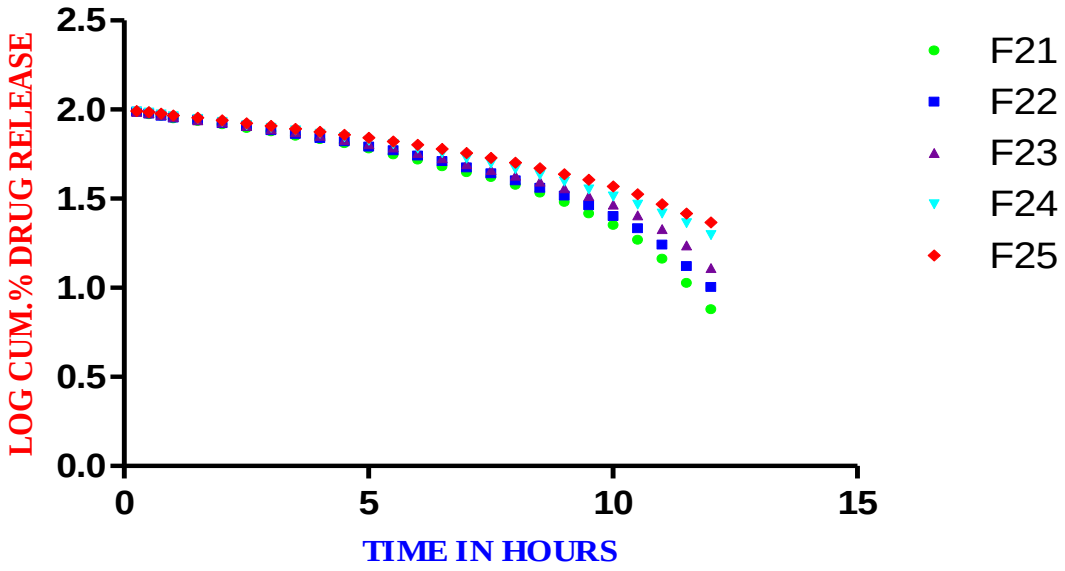


FIGURE 13f: COMPARISON OF FIRST ORDER RELEASE KINETICS OF FORMULATION CONTANING HPMC K15M AND XANTHAN GUM IN DIFFERENT RATIOS

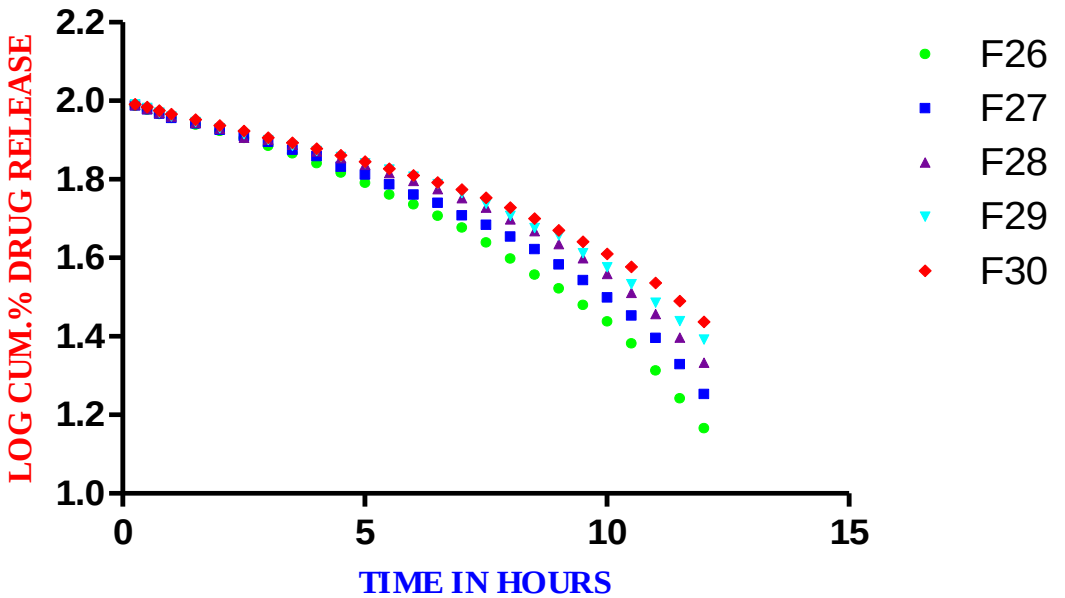


FIGURE 14a: COMPARISON OF HIGUCHI MODEL RELEASE KINETICS OF FORMULATION CONTAINING CARBOPOL AND HPMC K15M IN DIFFERENT RATIOS

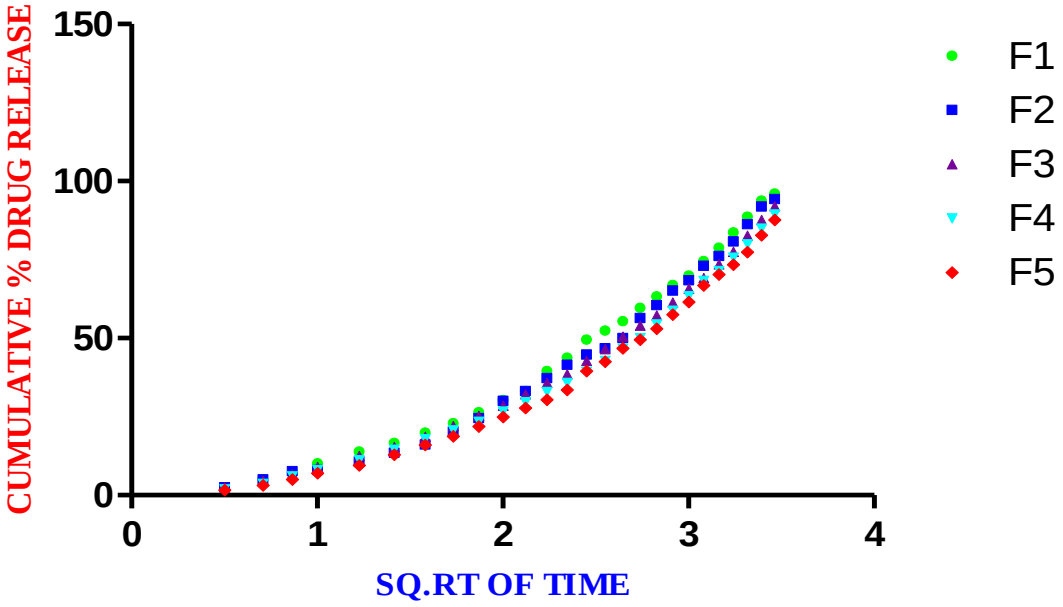


FIGURE 14B: COMPARISON OF HIGUCHI MODEL RELEASE KINETICS OF FORMULATION CONTAINING CARBOPOL AND XANTHAN GUM IN DIFFERENT RATIOS

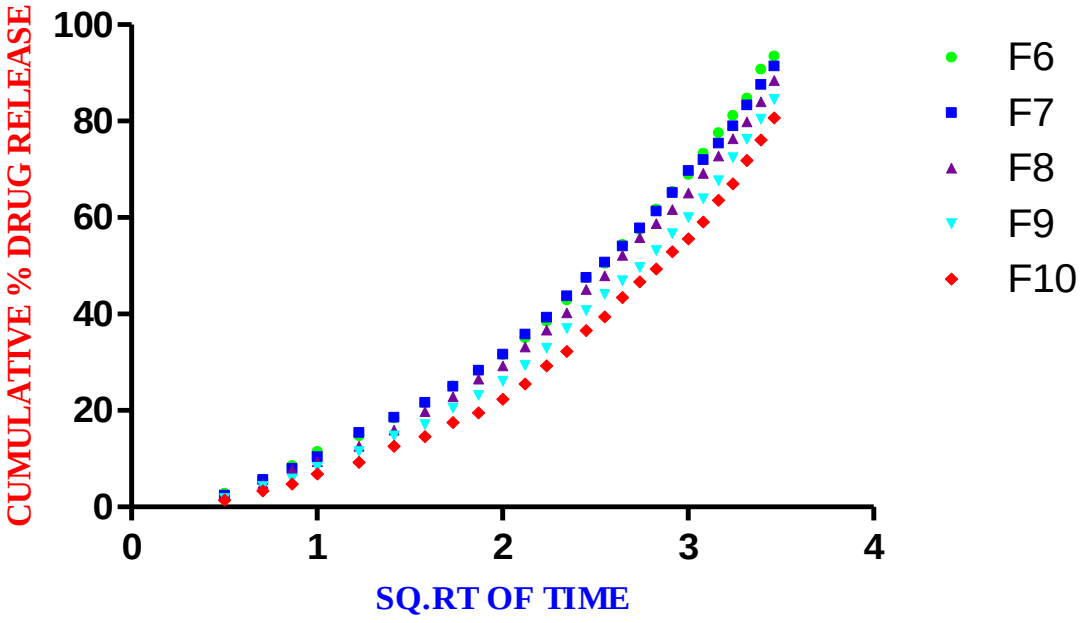


FIGURE 14c: COMPARISON OF HIGUCHI MODEL RELEASE KINETICS OF FORMULATION CONTAINING CARBOPOL AND CMC SODIUM IN DIFFERENT RATIOS

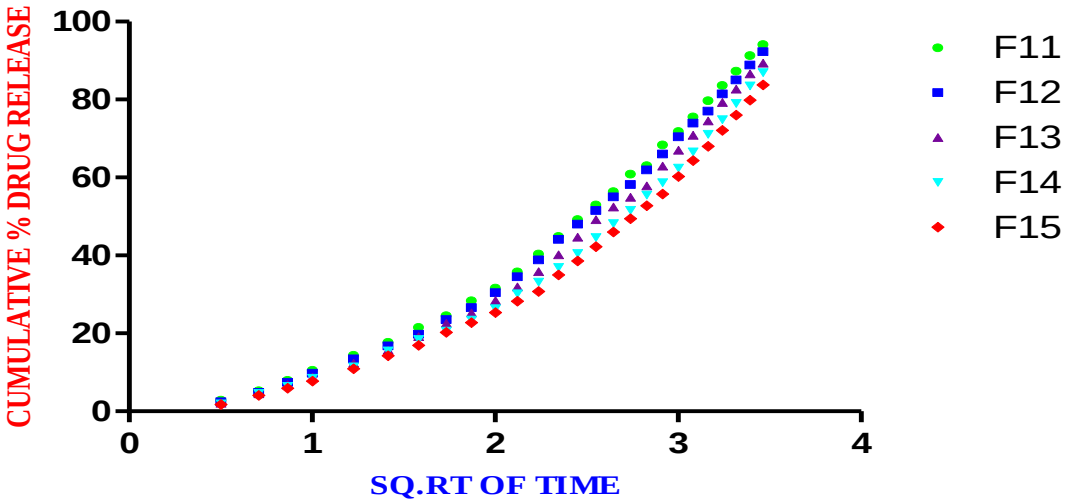


FIGURE 14d: COMPARISON OF HIGUCHI MODEL RELEASE KINETICS OF FORMULATION CONTAINING CARBOPOL AND CHITOSAN IN DIFFERENT RATIOS

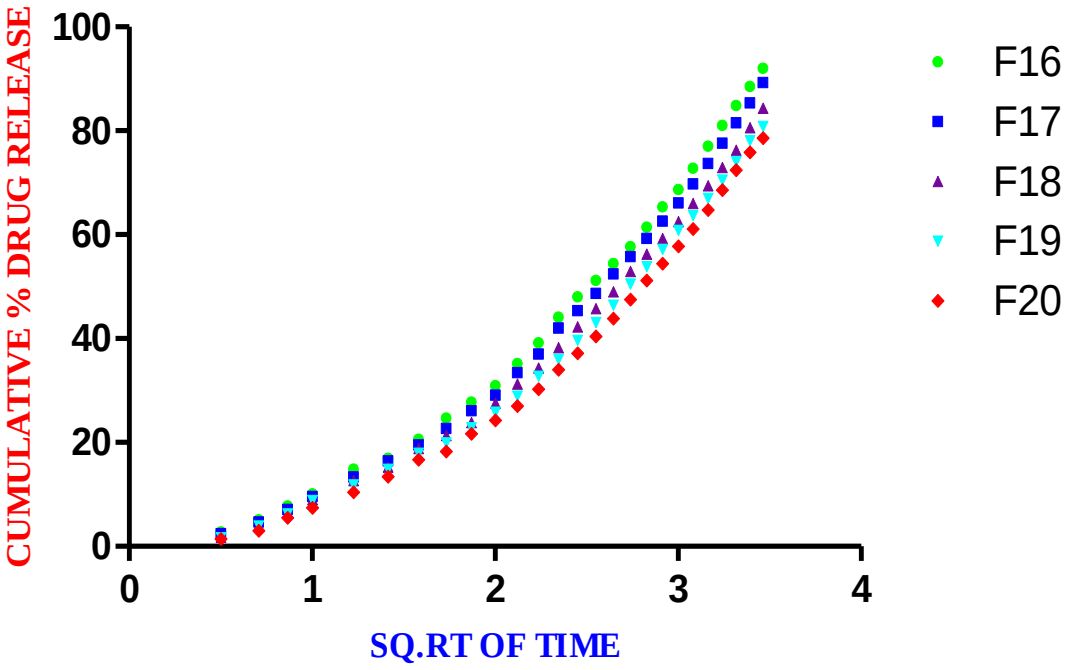


FIGURE 14e: COMPARISON OF HIGUCHI MODEL RELEASE KINETICS OF FORMULATION CONTAINING HPMC K15M AND CMC SODIUM IN DIFFERENT RATIOS

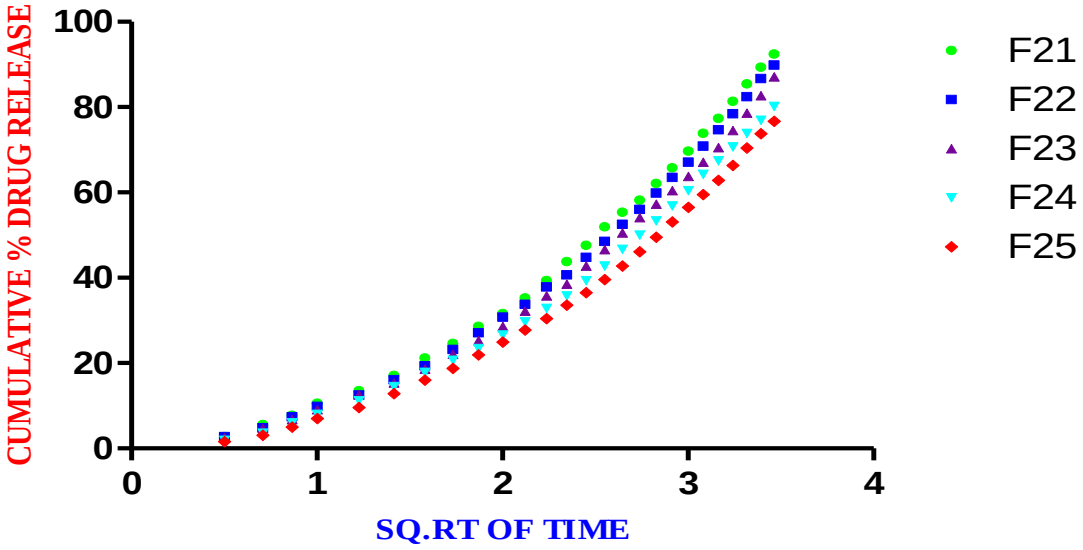


FIGURE 14f: COMPARISON OF HIGUCHI MODEL RELEASE KINETICS OF FORMULATION CONTAINING HPMC K15M AND XANTHAN GUM IN DIFFERENT RATIOS

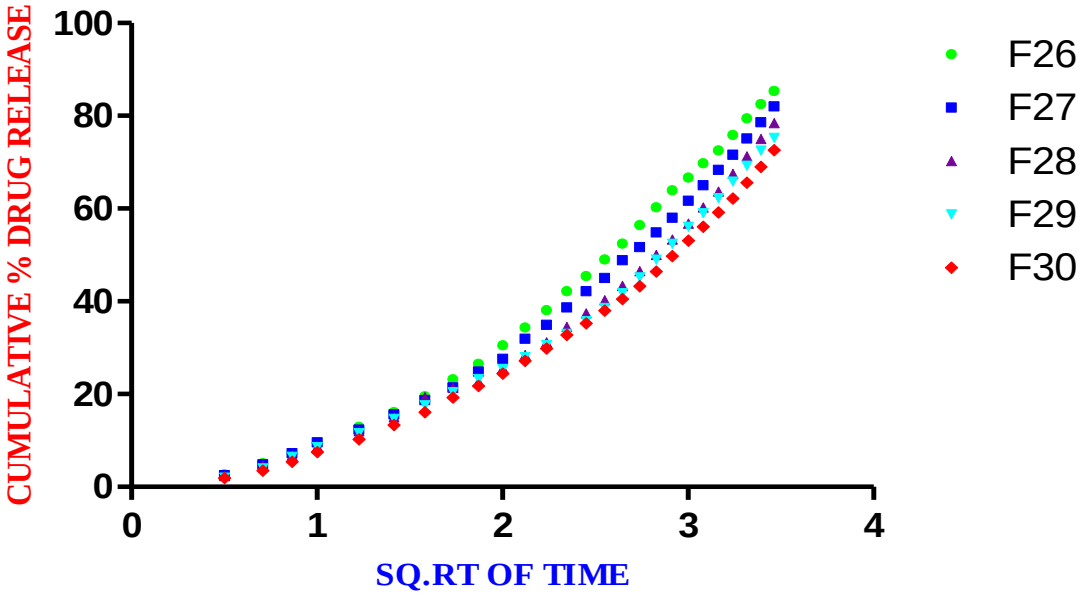


FIGURE 15a: COMPARISON OF HIXSON-CROWELL MODEL RELEASE KINETICS OF FORMULATION CONTAINING CARBOPOL AND HPMC K15M IN DIFFERENT RATIOS

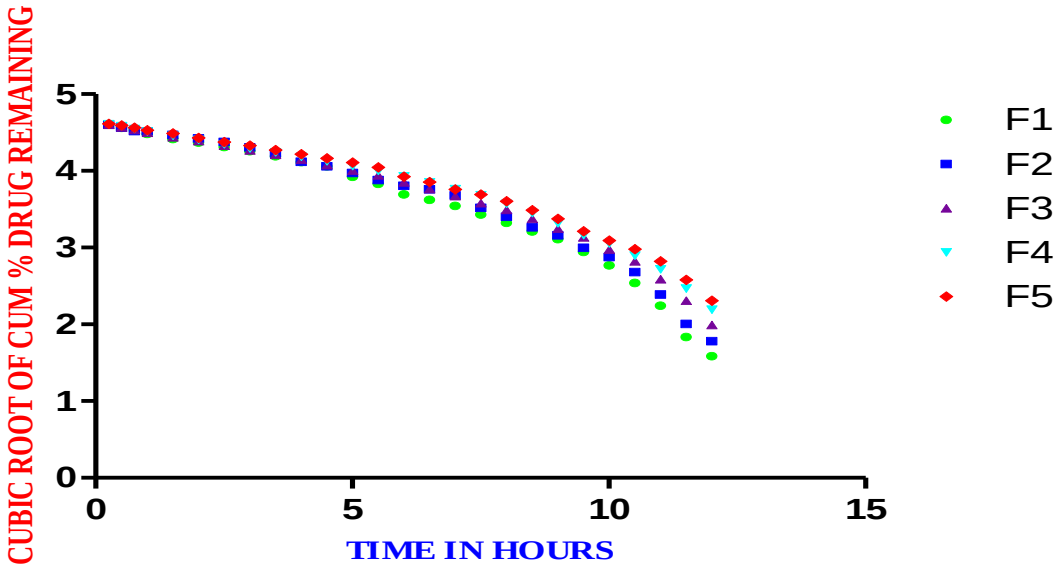


FIGURE 15b: COMPARISON OF HIXSON-CROWELL MODEL RELEASE KINETICS OF FORMULATION CONTAINING CARBOPOL AND XANTHAN GUM IN DIFFERENT RATIOS

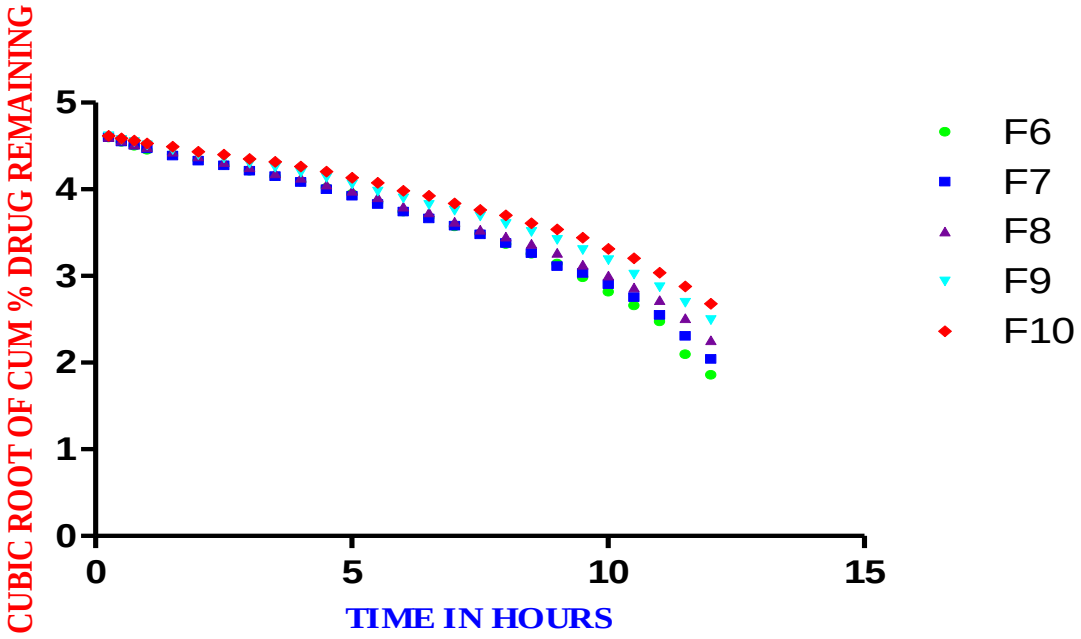


FIGURE 15c: COMPARISON OF HIXSON-CROWELL MODEL RELEASE KINETICS OF FORMULATION CONTAINING CARBOPOL AND CMC SODIUM IN DIFFERENT RATIOS

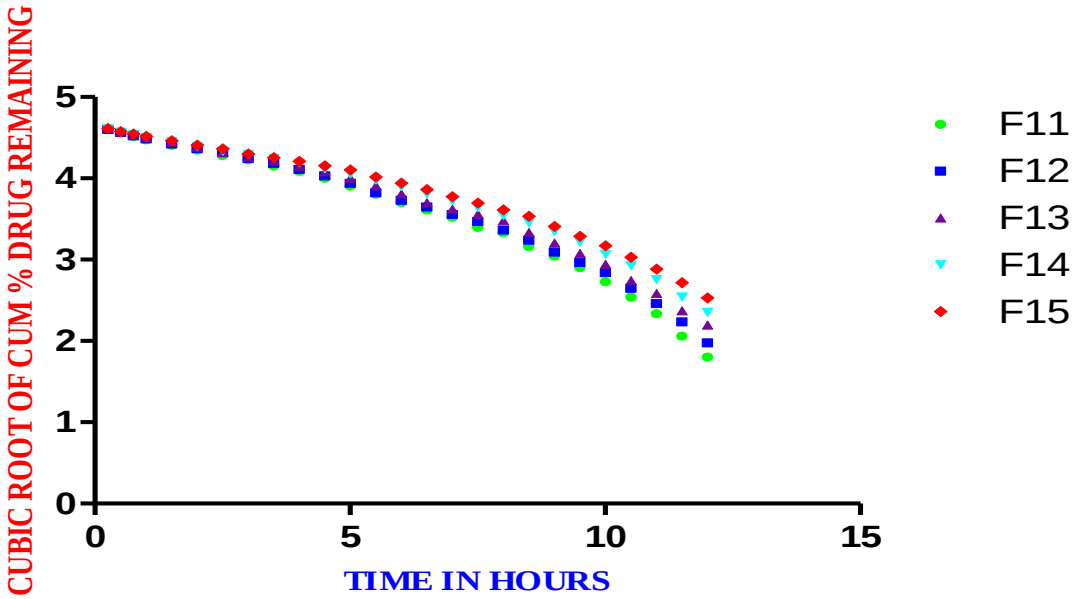


FIGURE 15d: COMPARISON OF HIXSON-CROWELL MODEL RELEASE KINETICS OF FORMULATION CONTAINING CARBOPOL AND CHITOSAN IN DIFFERENT RATIOS

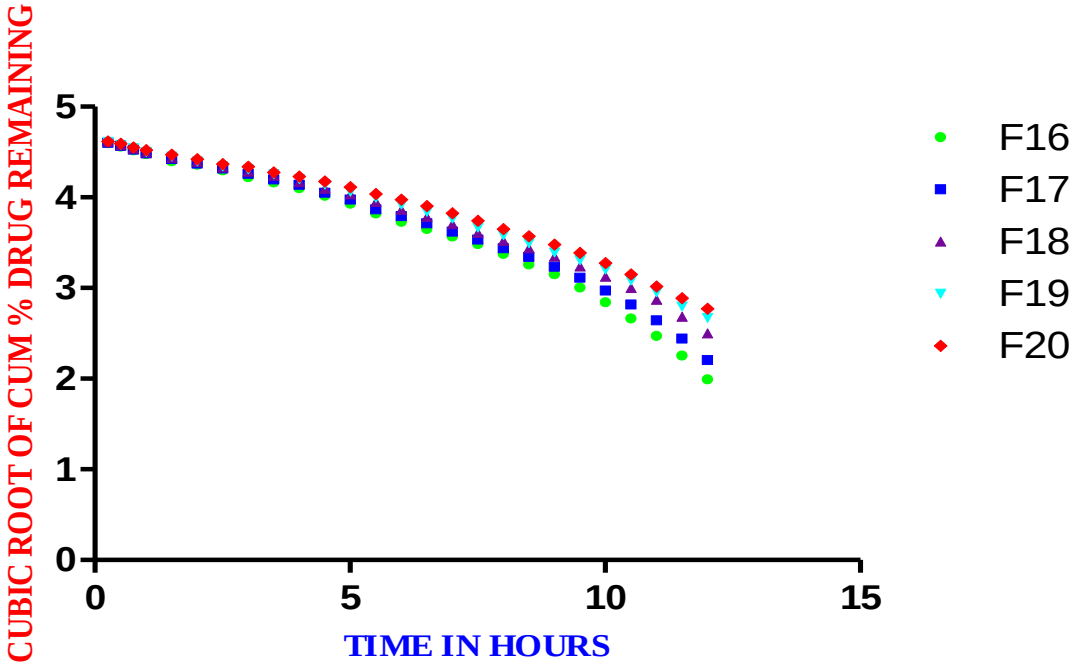


FIGURE 15e: COMPARISON OF HIXSON-CROWELL MODEL RELEASE KINETICS OF FORMULATION CONTAINING HPMC K15M AND CMC SODIUM IN DIFFERENT RATIOS

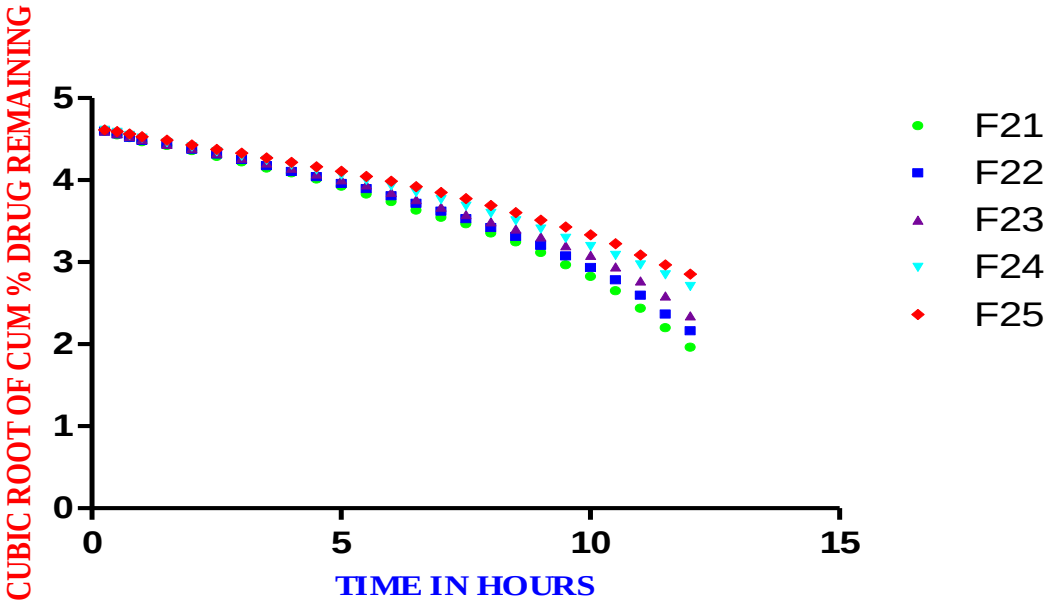


FIGURE 15f: COMPARISON OF HIXSON-CROWELL MODEL RELEASE KINETICS OF FORMULATION CONTAINING HPMC K15M AND XANTHAN GUM IN DIFFERENT RATIOS

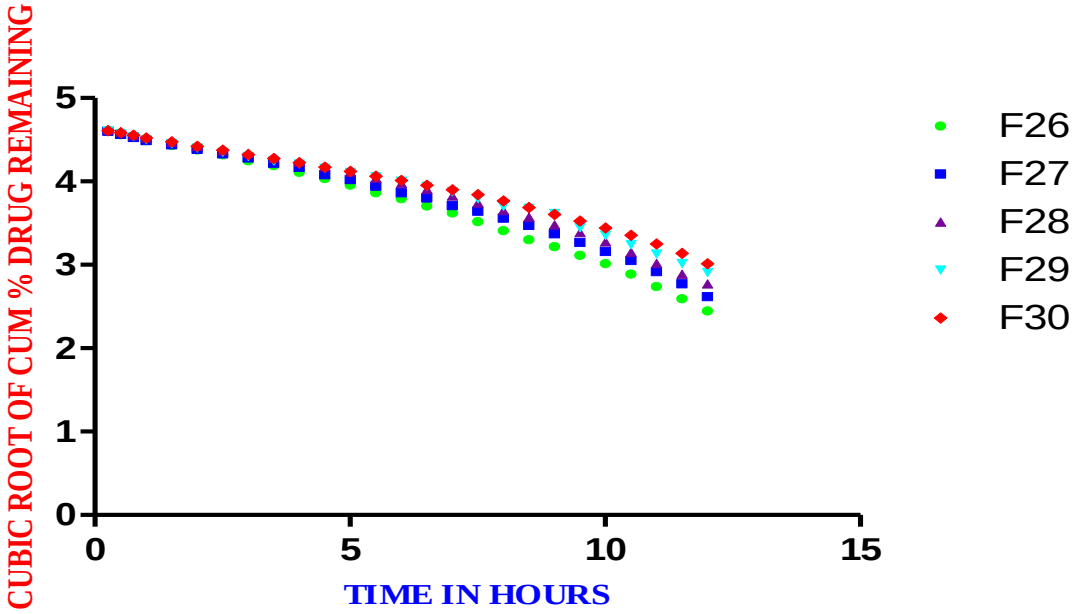


FIGURE 16a: COMPARISON OF KORSMEYER-PEPPAS MODEL RELEASE KINETICS OF FORMULATION CONTAINING CARBOPOL AND HPMC K15M IN DIFFERENT RATIOS

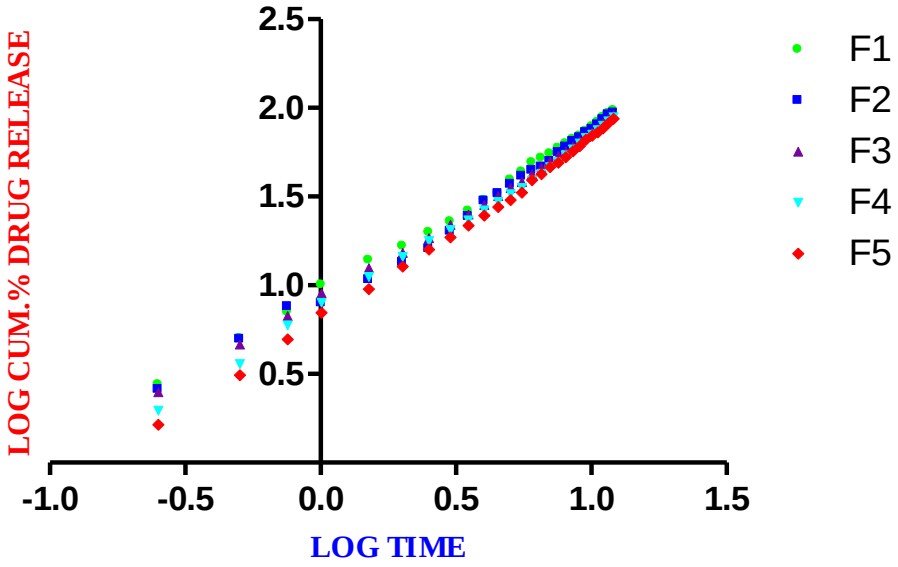


FIGURE 16b: COMPARISON OF KORSMEYER-PEPPAS MODEL RELEASE KINETICS OF FORMULATION CONTAINING CARBOPOL AND XANTHAN GUM IN DIFFERENT RATIOS

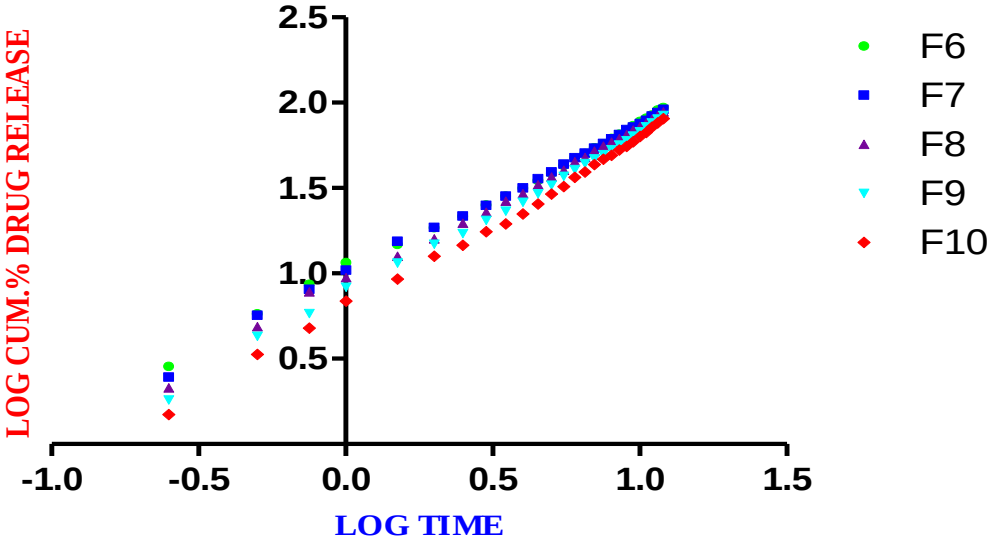


FIGURE 16c: COMPARISON OF KORSMEYER-PEPPAS MODEL RELEASE KINETICS OF FORMULATION CONTAINING CARBOPOL AND CMC SODIUM IN DIFFERENT RATIOS

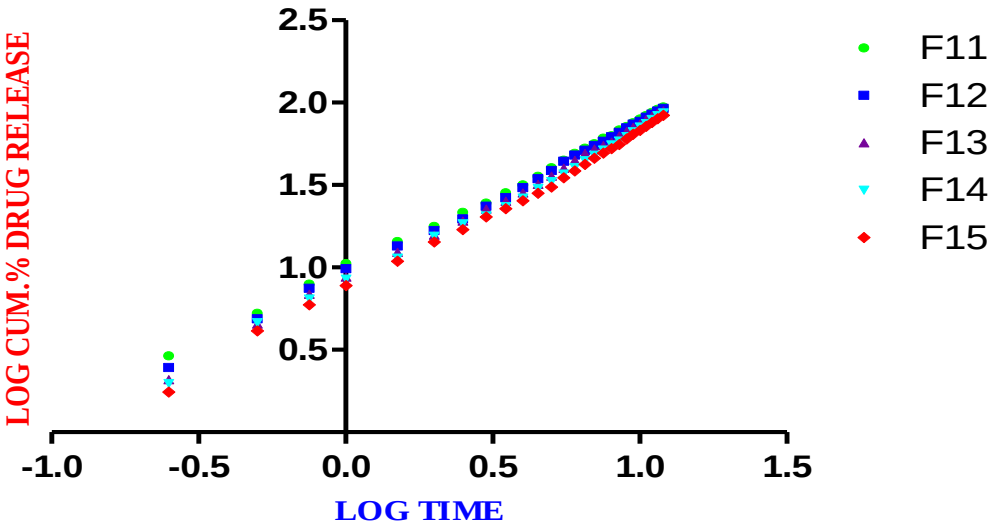


FIGURE 16d: COMPARISON OF KORSMEYER-PEPPAS MODEL RELEASE KINETICS OF FORMULATION CONTAINING CARBOPOL AND CHITOSAN IN DIFFERENT RATIOS

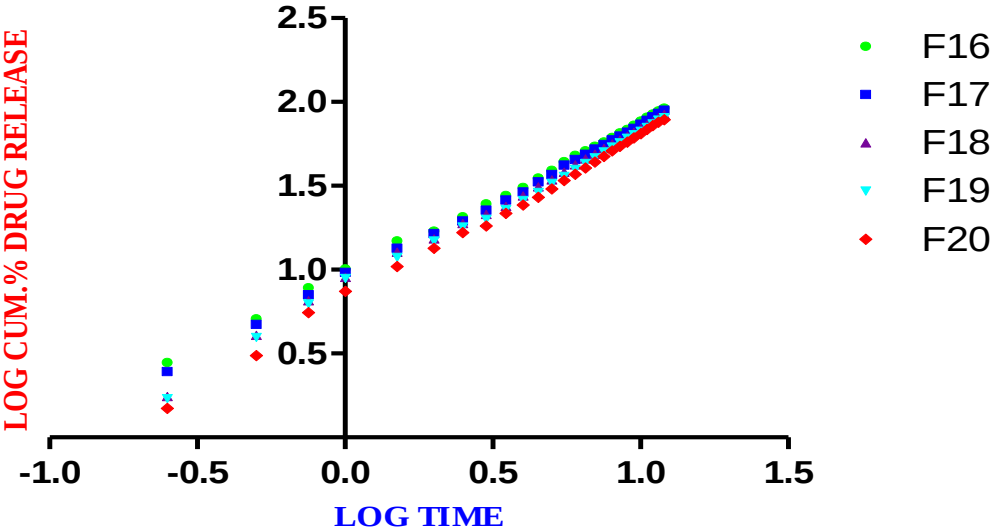


FIGURE 16e: COMPARISON OF KORSMEYER-PEPPAS MODEL RELEASE KINETICS OF FORMULATION CONTAINING HPMC K15M AND CMC SODIUM IN DIFFERENT RATIOS

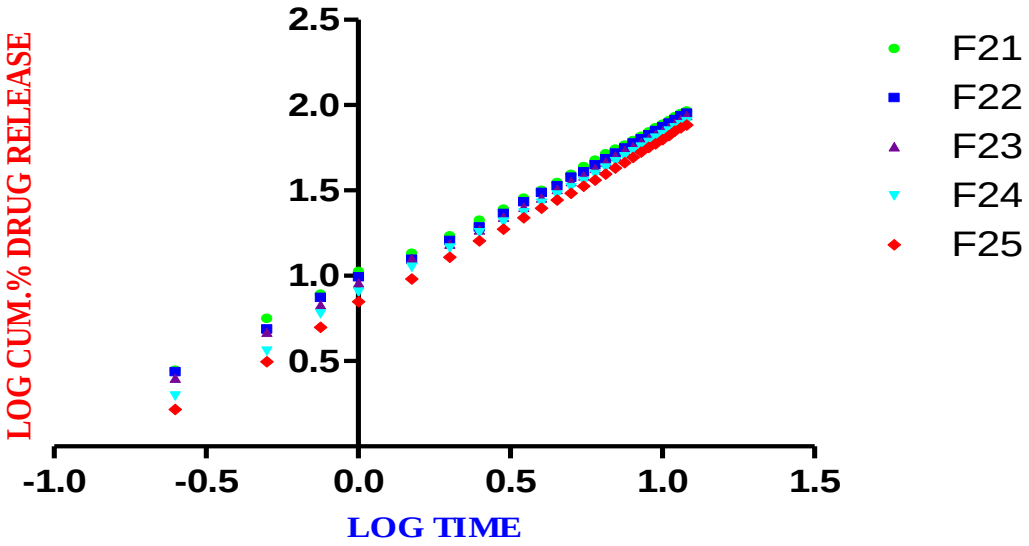
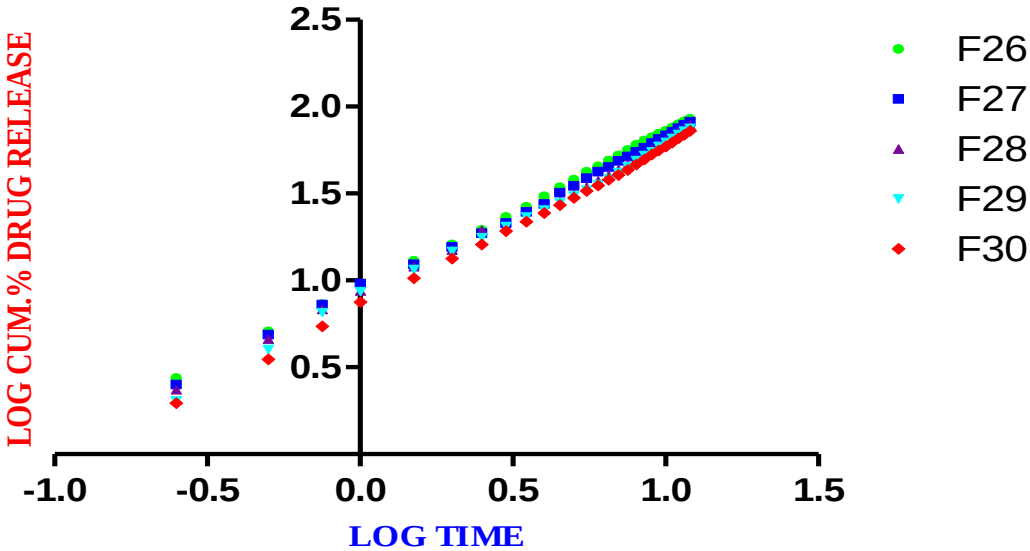


FIGURE 16f: COMPARISON OF KORSMEYER-PEPPAS MODEL RELEASE KINETICS OF FORMULATION CONTAINING HPMC K15M AND XANTHAN GUM IN DIFFERENT RATIOS



CHAPTER XI

SUMMARY AND CONCLUSION

CHAPTER XI

SUMMARY AND CONCLUSION

- The objective of the present investigation was to develop olmesartan buccal adhesive tablet to achieve controlled release and improve the bioavailability, by retarding its extensive hepatic first pass metabolism.
- FTIR studies indicated that there was no interaction between drug and excipients.
- Buccal adhesive tablets were prepared by direct compression method by using different ratios of hydrophilic polymers such as carbopol 934P, HPMC K15M, CMC sodium, xanthan gum and chotosan.
- The formulated tablets were evaluated for pre compression & post compression parameters viz mucoadhesive strength, in vitro drug release, swelling index, surface pH, drug release kinetics & stability studies.
- The pre compression parameter of all the formulations was within the required limit that was suitable for formulation of the tablets.
- The post compression parameters such as hardness, thickness, friability, uniformity in weight, drug content & mucoadhesive strength of all the formulated tablets were within the acceptable limits.
- Drug release rate was increased with increasing amount of hydrophilic polymer. High water uptake which leads to considerable swelling of polymer and causes drug to diffuse out from polymer matrix. Moreover the hydrophilic polymers would leach out and hence creates more pores and channels for drug to diffuse out from the device.
- The *in vitro* release studies revealed that the formulation F1 (Carbapol 934P and HPMC K15M in 2.5:1 ratio) was selected as best formulation which had

the better controlled release (96.01% in 12 hours) and subjected to further studies.

- The *in vitro* drug release kinetics studies of all the formulations followed zero order kinetics and Non-Fickian diffusion mechanism.
- IR studies of best formulation (F1) indicated there was no interaction between the drug and excipients.
- The selected formulation was found to be stable under the storage condition.

CONCLUSION

Olmesartan medoxomil buccal adhesive tablets could be formulated using the drug and hydrophilic mucoadhesive polymers such as carbopol 934P, HPMC K15M, CMC sodium, xanthan gum and chotosan in different ratios. Among all the formulations F1 showed satisfactory results for swelling behaviour, mucoadhesive strength and maximum drug release profile for 12 hours in a controlled manner. Drug release kinetic result reveals that all the formulations follow zero-order kinetics and Non-Fickian diffusion mechanism. The olmesartan medoxomil buccal adhesive tablets may be a good way to bypass the extensive hepatic first-pass metabolism and to improve the bioavailability of olmesartan through buccal mucosa.

REFERENCES

REFERENCES

Ananda Reddy. K., Venugopal. K., 2012. Formulation and evaluation of buccal tablets of piroxicam. *Int. J. Chem. Sci.* 10(1), 399-412.

Bhanja Satyabrata., Elaiah. P., Mohanty Chandran., Murthy K.V.R., 2010. Design and in-vitro evaluation of mucoadhesive buccal tablets of perindopril prepared by sintering technique. *International journal of pharmtech research.* Vol.2, 1810-1823.

Deelip Derle., Omkar Joshi., Ashish Pawar., Jatin Patel., Amol Jagadale., 2009. Formulation and evaluation of buccoadhesive bi-layer tablet of propranolol hydrochloride. *International journal of pharmacy and pharmaceutical sciences.* Vol. 1, 206-212.

Shashikant D., Barhate., Kandarp M. Patel,, Ganeshkumar S. Lokhande., 2011. Formulation and evaluation of buccoadhesive tablet of Atenolol. *Der Pharmacia Lettre.* 3(2), 34-38.

Ravi Krishna. Y., Madhusudhan Rao., Chinna Reddy.K., Sujatha., 2011. Formulation and *invitro* evaluation of buccoadhesive tablets of furosemide. *International journal of drug development & research.* Vol. 3, 351-361.

Vijaya muthumanikandar., Sudeesh Edavalath., Jerry Heison Robert., Raka Mukerghee., Vaneesh., 2011. Development and *in- vitro* evaluation of buccoadhesive tablets of losartan potassium. *International journal of drug delivery.* 3, 465-471.

Muthukumaran. M., Dhachinamoorthi., Chandra sekhar. B., 2012. Fabrication and evaluation of sustained release mucoadhesive bilayer tablets containing nifedipine. *Der pharmacia sinica.*3(3), 367-376.

Hiremath.JG., Sarfaraz. MD., Hiremath. D., Sarudkar. SA., 2009. Preparation and physicochemical characterization of simvastatin loaded mucoadhesive bilayered tablet. *Indian journal of novel drug delivery.*1(1), 18-24.

Gaiah Goud. B., Kumara swamy. S., Praveen kumar. V.,2011. Formulation and evaluation of bioadhesive buccal tablets of simvastatin. *Journal of advanced pharmaceutical sciences.*Vol.1, 29-39.

Guda Aditya., Ganesh Kumar Gudas., Manasa Bingi., Subal Debnath., Rajesham. V.V., 2010. Design and evaluation of controlled release mucoadhesive buccal tablets of lisinopril. *International journal of current pharmaceutical research.* Vol 2, 24-27.

Manivannan. R., Balasubramaniam. A., Prem Anand. DC., Sandeep. G., Rajkumar. N., 2008. Formulation and in-vitro evaluation of mucoadhesive buccal tablets of diltiazem hydrochloride. *Research J. Pharm and tech.* 1(4), 478-480.

Margret chandira., Palanisamy. P., Jayakar. B., Rajesh Chatakonda., 2009. Design and development of controlled release mucoadhesive oral tablet of clarithromycin. *International journal of pharma recent research.* 1(1), 59-66.

Ranade A.N., Ranpise N.s., Sanap G.S., Kulkarni R.R., 2011. Development and in-vitro evaluation of buccal tablet of quinapril hydrochloride. *Indian journal of pharmaceutical education and research.* Vol 45, 364-369.

Raviteja Achanta., Pujanitheesha Morampudi., Dineshbabu., Vamshikrishna., Nagendrarao Kukalakunta., 2013. Development and in-vitro evaluation of buccoadhesive bilayer tablets of thiocolchicoside. *Mintage journal of pharmaceutical and medical science.* Vol.2, 41-44.

Raghavendra Rao. N.G., Gururaj. S., Kulkarni., 2012. Formulation and evaluation of mucoadhesive buccal bilayered tablets of sabutamol. *International journal of drug development and research.* 4(4), 375-384.

Sellappan Velmurugan., Kiran Kumar., Raghavarapu., 2013. Formulation and in-vitro evaluation of glipizide mucoadhesive buccal tablets. *International journal of pharma and bio science.* 4(2), 594-607.

Satyabrata Bhanja. C., Zukiuddin Shafeeque. M.D., Muvvala Sudhakar., 2013. Mucoadhesive buccal tablets of glimipride- formulation and evaluation. *International journal of pharmacy and pharmaceutical sciences.* Vol 5, 502-510.

Satyabrata Bhanja., Ellaiah. P., Sujit Kumar Martha., Pratit Kanchan Sahu., Sandip Prasad Tiwari., Bibhuti Bhusan Panigrahi., Debajhoti Das., 2010. Formulation and in-vitro evaluation of mucoadhesive buccal tablets of timolol maleate. *Int J pharma biomed res.* 1(4), 129-134.

Suresh Kumar P., Srikanth. B., Shaji. G., Navaneetha Krishnan. S., Saranya. P., 2011. Formulation and evaluation of nebivolol mucoadhesive buccal tablets. *Pharmacologyonline* 3, 869-885.

Shiva Krishna. S., Subhabrata Ray., Thakur R.S., 2006. Formulation and evaluation of mucoadhesive dosage form containing rosiglitazone maleate. *Pak. J. pharm. Sci. Vol.* 19(3), 208-213.

Bhaskar Umarji., Rudragouda Patil., Ravindra Birajdar., Swati Mysore., Siddramesh Bilagi., Dhananjay audurti., 2012. Formulation and evaluation of mucoadhesive buccal tablets of furosemide. *World journal of pharmacy and pharmaceutical sciences.* Volume 1, 1041-1063.

Raviteja Achanta., Chandra. S., parthiban. K.G., Naveen Raja Kande., Devareddy Sandeepo., 2012. Development and in-vitro evaluation of buccodhesive tablets of losartan potassium. *International research journal of pharmacy.* 3(9), 277-281.

Gaurav kumar., samita Gauri., Aashima Hooda., Sangita Saini., Arun Garg., 2011. Fabrication and evaluation of flavoured mucoadhesive buccal tablet of caffeine as CNS stimulant. *International journal of universal pharmacy and life sciences.* 1(3), 85-97.

Goswami Dhruba Sankar., Goyal Sandeep., Sharma Rani., Mehta Naveen., Puja Kumari., Kunwar S Pramod., 2011. Formulation and evaluation of mucoadhesive tablets of famotidine. *Journal of pharmaceutical and biomedical sciences.* 12(60), 1-3.

Shashikant D. Barhate., KAndarp M. Patel., Ganeshkumar.S., Lokhande., 2011. Formulation and evaluation of buccoadhesive tablets of atenolol. *Der pharmacia letter.* 3(2), 34-38.

Basawaraj S. Patil., Sandeeep S. Tate., Upendra Kulkarni., Srinivas R. Soodam., Prasad A. Vedpathak., 2011. Development and in-vitro evaluation of mucoadhesive buccal tablets of tizanidine hydrochloride using natural polymer guar gum. *International journal of advances in pharmaceutical sciences.* Vol. 2(2-3), 189-198.

Balamurugan.M., Saravanan VS., Ganesh P., Senthil SP., Hemalatha PV., Sudhir Pandya., 2008. Development and in-vitro evaluation of mucoadhesive buccal tablets of domperidone. *Research J. pharm and Tech.* 1(4), 377-380.

Appa Rao Potu., Naresh Pujari., Shashidher Burra., Prabhakar Reddy Veerareddy., 2012. Formulation and evaluation of buccoadhesive tablets of quetiapine fumarate. *Brazillian journal of pharmaceutical sciences.* Vol. 48, 335-345.

John D.Smart., 1993. Drug delivery using buccal-adhesive systems. *Advanced drug delivery reviews.* Vol.11, 253-270.

Pankil A. Gandhi., Patel M.R., 2011. A review article on buccal adhesive drug delivery system. *International journal of pharmaceutical research and development.* Vol. 3(5), 159-173.

Thomas P. Johnson., Nazila Salamat-Miller., Montakarn Chittchang., 2005. The use of mucoadhesive polymers in buccal drug delivery. *Advanced drug delivery reviews.* 57, 1666-1691.

Anay R. Patel., Dhagash A Patel., Sharad V. Chaudhry., 2011. Mucoadhesive buccal drug delivery system. *International journal of pharmacy and life sciences.* Vol. 2(6),848-856.

Santanu Roychowdhury., Rajesh Gupta., Sourav Saha., 2011. A review on buccal mucoadhesive drug delivery systems. *Indo global journal of pharmaceutical sciences.* Vol. 1, 223-233.

Vinod KR., Rohit Reddy T., Sandhya S., David Banji., Venkatram Reddy B., 2012. Critical review on mucoadhesive drug delivery systems. *Hygeia. J. D. Med.* Vol.4(1), 7-28.

Amit Alexander., Ajazuddin., Swarna., Mukesh Sharma., Tripathi D. K., 2011. Polymers and permeation enhancers: specialized components of mucoadhesives. *Stamford journal of pharmaceutical sciences.* Vol. 4(1), 91-95.

Punitha S., Girish Y., 2010. Polymers in mucoadhesive buccal drug delivery system-*A review. Int. J. Res. Pharm. Sci.* Vol. 1, 170-186.

Keiko Tsutsumi., Yasuko obata., Tsuneji Nagai., Thorsteinn Loftsson., Kozo Takayama., 2002. Buccal absorption of ergotamine tartrate using the bioadhesive tablet system in guinea-pigs. *International journal of pharmaceuticals.* 238, 161-170.

Sumitha Singh., Vikas Bali., Kamla Pathak., 2011. Development and validation of novel spectrophotometric analytical method for the determination of olmesartan in pharmaceutical formulations. *International journal of pharmacy and pharmaceutical sciences.* Vol. 3, 487-490.

Gil Yosipovitch., Ilana Kaplan., Shlomo Calderon., Michael David., Yiong Huak Chan., Abraham Weinberger., 2001. Distribution of mucosal pH on the buccal cavity. *Acta Derm Venerol.* 81, 178-180.

Ashwini A. Yadav., Dhanashri S Yadav., Poonam S Karekar., Yogesh V Pore., Pankaj Gajare., 2012. Enhanced solubility and dissolution rate of olmesartan medoxomil using crystallo-co-agglomeration technique. *Der Pharmacia Sinica.* 3(2), 160-169.

Abdullah Al Masud., Mahfuzur Rahman., Moynul Hasan., Kamal Hossain Ripon., Ahsanur Rahman., Rabiul Islam., Raihan Sarkar., 2012. Validated spectrophotometric method for olmesartan medoxomil in pharmaceutical formulation. *International journal of pharmaceuticals and life sciences.* Vol.1, 1-7.

Shivanand K., Raju S. A., Jaykar B., 2010. Mucoadhessive bilayered buccal tablets of tizanidine hydrochloride. *International journal of pharmTech Research.* Vol.2, 1861-1869.

Ankarao A., Jitendra kumar. P., Babu rao., Devanna. N., Venkata Phani Deepthi. B., 2011. Formulation and evaluation of buccoadhesive bilayered tablets of carvedilol. *International journal of pharmaceutical, chemical and biological sciences*. 1(1), 6-11.

Yadav Deepak R., Ayyappan T., Shanmugam S., Sundaramoorthy K., Vetrichelvan T., 2011. Development and in-vitro evaluation of buccoadhesive metoclopramide hydrochloride tablet formulations. *International journal of pharmTech research*. Vol. 3, 516-525.

Gururaj. S Kulkarni., Raghavendra Rao N. G., Narasimhareddy D., 2013. Formulation development and evaluation of terbutaline sulphate mucoadhesive buccal tablets. *Int. Res. J. Pharm.* 4(3), 189-192.

Muthadi Radhika., Vamshi Raj., Reddy M.V.R., 2013. Formulation and in-vitro evaluation of buccoadhesive bilayer tablets of enalapril maleate. *IJIPSR.* 1(1), 96-108.

Vamsi Krishna Murthy G., Narasimharao B.V., Gayathridevi K., Pavani G., Harikrishna., 2013. Formulation and evaluation of carvedilol bilayered buccal adhesive tablets by direct compression technique**.** *International journal of pharmacy and pharmaceutical science research.* 3(2), 61-66.

Raut D.B., Sakhare R.S., Kankudte A.D., Muli P.N., Bharkad V.B., 2013. Formulation and *in vitro* evaluation of mucoadhesive buccal tablet of losartan potassium using synthetic

and natural polymers. *World journal of pharmaceutical research.* Vol. 2, 1577-1590.

Praveen.G., 2012. Development and *in vitro* evaluation of buccoadhesive

tablets of losartan potassium. *The pharma innovation.* Vol.1, 63-70.

Muthukumaran. M., Dhachinamoorthi. D., Chandra Sekhar. K.B., 2013. Development and optimization of hydralazine HCl sustained release mucoadhesive buccal tablets using 2^3factorial design. Int J Adv Pharm Gen Res. 1(2), 20-32.